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ORIGINAL ARTICLES

COMPARATIVE VALUE OF THE METHODS OF TREATING TETANUS.[1]

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This study will not deal with (1) the prophylactic treatment of tetanus, (2) the surgical treatment of the wound or condition underlying the tetanus, (3) the general sedative treatment. The omission of these subjects is not due to any lack of recognition of their importance or necessity, but for the sake of brevity it is assumed that the last two requirements will be carried out so thoroughly as feasible.

My personal experience in the treatment of tetanus is limited to 8 cases; 3 cases died while 5 survived. Of these the first 2 fatal cases did not have the benefit of the more modern or radical methods, whereas the last 6 are characterized by having received antitoxin intraspinally. Of these 6 cases so treated since 1907 only 1 died, a mortality of 17 per cent. The following is a history of the cases, and I add one treated by my colleague, Dr. J. C. Roper, on the First Medical Division of the New York Hospital, which he has kindly allowed me to utilize:

Case I.—Sarah B. Previous operation by me for ovarian cyst. Convalescence normal. Operation at the General Memorial Hospital September 5, 1902, for similar condition. Convalescence

[1] Read before the American Surgical Association, Washington, D. C., May 10, 1916.

normal up to September 16; wound healed by primary union. That day pain in shoulder and back developed, with pain and stiffness in masseters. September 17, 20 c.c. of tetanus antitoxin was administered subcutaneously every six hours. There was general muscular twitching. From September 17 to day of death, September 23, patient kept quiet with morphin. Muscular rigidity general, most pronounced along spine. Masseters relaxed after 40 c.c. of tetanus antitoxin had been given. There is no definite record of the exact amount of antitoxin given or its equivalent in units. Incubation not known. If infection began at time of operation it would be eleven days; if it were due to liberation of tetanus organisms contained in the catgut allowance would have to be made for the disintegration of the catgut. Antemortem temperature, 109.8°. Tetanus developing after an abdominal operation rarely, if ever, recovers.

CASE II.—John E. Policeman. Admitted to St. Luke's Hospital January 28, 1905. Died in twenty-four hours.

Present History. In attempting to stop a runaway horse he was thrown to the ground, cutting the little finger of his right hand. (Exact date of incubation unknown, but very acute.)

Chief Complaint. Irrational, convulsions.

Physical Examination. Head drawn back and neck and back rigid. Jaws fixed. Arms and legs are stiff. On dorsal aspect of terminal phalanx of right little finger there is a lateral wound.

Operation. Amputation of little finger. Exposure of brachial plexus and injection of 20 c.c. of tetanus antitoxin into nerves. Wound left open for future similar injections. Shortly after operation patient had slight convulsive contraction affecting entire body. At 1.45 A.M., January 29, severe convulsion. Patient very cyanotic. 9.45 A.M., dressing removed. 20 c.c. of tetanus antitoxin injected into the axillary nerves. 11 A.M., severe muscular contraction; patient died.

CASE III.—Joseph G., aged forty years. Admitted to Hudson Street Hospital May 28, 1907. Discharged June 23, 1907. One week before admission, while at work, patient caught his right hand in a press, causing a severe compound fracture of the tip of the right thumb and the right index finger. The index finger was amputated at the metacarpal phalangeal joint, the operation being done in the dispensary. Patient returned daily for dressings, and was apparently improving, when on the day of admission he complained of stiff jaw, being unable to open his mouth more than a half inch. On May 29 the right brachial plexus was exposed under a general anesthetic and 60 c.c. of tetanus antitoxin injected into the nerve sheath. On May 31 two 20 c.c. doses of tetanus antitoxin were injected intravenously. Still marked rigidity of muscles of the cheeks, neck, and back. These were repeated on June 1. On June 2 still marked rigidity of back and thighs. Patient had involuntary spasms

of the muscles of the thigh, causing him much pain. These spasms involved all muscles of the lower extremities. Patient was not incontinent at any time. Did not suffer with retention. Could move forearm freely, but movements of the right shoulder were less free, giving some discomfort. From June 3 to 11, 20 c.c. of antitoxin was injected intravenously daily (except June 6, 8 and 10). On June 12 there was marked improvement. Muscles of cheek, neck, and back less irritable and spastic. Thighs still rigid on slight palpation. On June 15 condition was much better. There was less rigidity in the thigh and the patient could open his mouth better and could flex the knees and thighs. Discharged cured June 23. Total amount of antitoxin 260 c.c., or 19,500 units (New York City Board of Health). Incubation unknown.

CASE IV.—Edward Mc., aged thirty-four years. Admitted to Hudson Street Hospital June 10, 1908. Discharged July 2, 1908. Incubation not known. About one year ago an ulcer broke out on the right leg. It has been healed up twice but recurred. Slept last night in the park. Felt all right when he went to sleep, but when he awoke this morning his legs felt stiff and numb as "if asleep." Sat a while to rest them, and when he started away he fell, and because of stiffness of his legs and thighs was unable to rise. Found by ambulance surgeon doubled up on the curbstone. During the day he has had no pain, but every time he has endeavored to stand his legs would cramp and the muscles become tense and hard, also the pectoral muscles would cramp from time to time. He thinks that for the past two days he has had difficulty in swallowing. He had nothing to eat all day today, so did not notice anything the matter with his jaws. On June 11, 1500 units of tetanus antitoxin were injected intravenously. Two later doses of 1500 units each. He received daily thereafter until June 17, 1500 units of antitoxin (Board of Health) subcutaneously and 1500 units intravenously. June 18 and 19 the 3000 units were all given subcutaneously. On June 23 the patient was considered cured and he was discharged June 30 in excellent condition. Total amount of antitoxin 34,500 units; 15,000 units intravenously, 19,500 subcutaneously.

CASE V.—John F., aged four years. Admitted to St. Luke's Hospital April 1, 1909. Died April 11, 1909. Run over by a street car and was dragged for some distance, the wheels passing over his left foot. Foot severely lacerated; all the phalanges were crushed and traumatically amputated. Both femora were fractured. On April 6, amputation at the lower third of the leg. April 8, 11.45 A.M., signs of tetanus first appeared. 7 P.M., 600 units of tetanus antitoxin were given intravenously. At 9.15 P.M., under chloroform anesthesia, the anterior crural nerve of the left thigh and its three branches were exposed. The nerve sheath was injected with 150 units of tetanus antitoxin. Sciatic nerve on left side exposed and sheath injected with 150 units. April 9, 1500 units of antitoxin

were injected into the abdominal wall. Patient unable to open jaws at all. At midnight ℳvii tetanus antitoxin were given in the anterior crural and sciatic nerves. April 10, 1500 units were injected into the abdominal wall (9.30 A.M.); 12 M., ℳvii tetanus antitoxin were injected into the sheath of the anterior crural nerve on the left side and the sheath of the sciatic nerve; 8.30 P.M., 500 units of tetanus antitoxin injected intravenously; 10.45 P.M., 800 units of tetanus antitoxin were injected into the abdominal wall. Patient died April 11 at 7 A.M. Incubation seven days.

CASE VI.—Thomas B., aged thirty-two years. Admitted to the New York Hospital April 1, 1914. Discharged April 30, 1914. Incubation ten days. On day of admission the patient was caught between a train and the foundation wall at the Pennsylvania Station. Extensive laceration and traumatic amputation of all the toes of the right foot. Two days after admission the toes were amputated. Ten days after admission (eight days after operation) first signs of tetanus—stiffness of jaws. Antitoxin treatment begun at once. It consisted of the following:

	Intraneural units.	Intravenous units.	Intramuscular units.	Intraspinal units.	Subcutaneous units.
April 11	1,500	3,500			
	3,000				
April 12	5,000	3,000			
	3,000	10,000	7000		
April 13	....	9,000	....	8000	3000
April 15	....	7,500			
April 17	....	5,000			
	12,500	38,000	7000	8000	3000

Total, 68,500 units.

Also three doses, 1 c.c. (1 per cent.) of carbolic acid.

Last injection of antitoxin given the sixteenth day after admission. Discharged twenty-nine days after admission, cured.

This was a very severe case with opisthotonos, general convulsions, and coma. In the single intraspinal injection, done April 13, 4 ounces of clear fluid were drawn off under marked increased pressure, followed by the injection of 8000 units into the spinal canal. It was followed by a temperature of 105.2° and temporary aggravation of symptoms, but on April 16 his condition improved markedly. On April 20 all symptoms disappeared, his mouth could be opened normally, and he was discharged in excellent condition April 30.

CASE VII.—Glen T., aged ten years. Admitted to the New York Hospital October 9, 1914. Incubation seven days. Seven days ago he ran a nail into the sole of his foot. On the day of admission the first signs of tetanus appeared. The family physician administered one injection of tetanus antitoxin and sent the boy to the hospital. On admission the jaws were tightly locked; tempera-

ture 100°. Two hours later 3000 units of antitoxin (Board of Health) were administered intraspinally and 1500 about the wound. Next day the temperature was 106° and the patient had frequent general convulsions. Condition continued critical, and on October 13, under chloroform anesthesia, 5000 units were injected intraspinally. It was noted that the fluid was milky in appearance. Temperature 104° next day, but on October 15 all symptoms abated and he improved rapidly. On October 19 he could open his mouth nearly normally, and was discharged October 24 rapidly gaining in strength, with all tetanic symptoms and signs entirely gone.

Summary of Antitoxin Treatment.

	Intraspinal units.	Intravenous units.	Subcutaneous units.
October 9	3000	10,000	1500
October 10	....	9,000	
October 13	5000		
	8000	19,000	1500

Total, 28,500 units.

Case VIII.—Henry S., aged twenty-eight years. Admitted to the New York Hospital September 5, 1915. Incubation seven days. History of having fallen from a tree the day before, a distance of fifteen feet, landing with the right forearm outstretched. Examination shows compound fracture of forearm with low grade of infection. First signs of tetanus appeared September 11, six days after admission. Patient could not open his mouth. Under a general anesthetic 5000 units of tetanus antitoxin were injected intraspinally, 10,000 units intravenously, and 5000 units subcutaneously. Subsequent intraspinal injections done under local anesthesia. On September 27 condition began to improve. On October 11 he could open his jaws about one-half their normal capacity. On October 18 all evidence of tetanus had disappeared, and he was discharged October 31 with tetanus cured.

Summary of Antitoxin Treatment.

	Intraspinal units.	Intravenous units.	Subcutaneous units.	
Sept. 11	5,000	10,000	5,000	5000 in vicinity
Sept. 12	4,000	10,000	5,000	of ulnar nerve.
		12,000		
Sept. 13	5,000	10,000		
Sept. 14	5,000	15,000		
Sept. 15	5,000	17,000		
Sept. 16	5,000	10,000		
Sept. 18	....	10,000	15,000	
Sept. 19	....	.....	1,000	
Sept. 20	....	15,000		
	29,000	109,000	26,000	

Total, 169,000 units.

This was a very severe case, complicated by a very extensive and severe compound fracture.

CASE IX.—Samuel N., aged twenty-four years. Admitted to the New York Hospital, service of Dr. J. C. Roper, September 5, 1915. Discharged September 25, 1915. Incubation three days (?). Patient was cut in palm of hand September 2 (three days before admission). Wound was dirty, but was well cleaned out and painted with iodin. That evening pain between the shoulders came on and the first signs of "lock-jaw." Since then these symptoms have grown steadily worse. On admission the neck is very stiff, both for lateral and anteroposterior movements. Cannot open the teeth more than 1.5 cm. Is unable to swallow. No history of convulsions. Superficial wound about 1.5 cm. long on the palm of the left hand. Not tender on pressure—not inflamed. On day of admission, under local anesthesia, lumbar puncture was done with injection of 3000 units of tetanus antitoxin intraspinally. This was repeated three times—(4500, 4500, and 5000 units). After the last injection, on September 8, he improved steadily. On September 12 the patient was up in a chair, and was discharged September 25, in good condition.

SUMMARY OF ANTITOXIN TREATMENT.

	Intraspinal units.	Intravenous units.
Sept. 5	1,500	10,500
Sept. 6	4,500	10,500
Sept. 7	4,500	10,000
Sept. 8	5,000	9,000
Sept. 9	....	15,000
Sept. 10	....	15,000
Sept. 11	....	15,000
	15,500	85,000

Total, 100,500 units.

Spinal fluid culture:
Sept. 5. Sterile five days.
Sept. 6. Sterile four days.
Sept. 7. Two spinal fluid cultures in agar tubes—both contaminated—Staphylococcus albus.

Although my personal experience is limited, I feel that the main reliance of the treatment of a well-marked case of tetanus should be along the lines employed in these last 4 cases, a combination of intraspinal and intravenous, also at the onset, local injection at the site of infection. With the more radical localization of the antitoxin in the nerve centers by the intraspinal method it seems to me unnecessary to make intraneural injections, and particularly if that procedure requires the administration of a general anesthetic and the time necessary for the careful dissection and exposure of the nerves. While the line of treatment outlined above impresses me most favorably, I realize that there are many divergent opinions, and that it is dangerous to draw conclusions from a limited

number of cases even though successful. Statistics regarding the favorable results of any kind of treatment for tetanus are open to all the objections attending statistical information. Undoubtedly the cases of tetanus vary very greatly in their severity. Certain cases might really be classified as hyperacute, and it is doubtful if they will ever give favorable results. Others are distinctly of a very mild or chronic type; sometimes of a recurring type. Generally speaking the period of incubation has a general prognostic import; that is, short incubations seem to give rise to consistently severe symptoms, and *vice versa*, but even with this standard as a basis there are a good many sources of error. An important factor is the severity of the underlying wound or injury and the kind of treatment it receives or can receive. For that reason it is difficult or impossible to make any very satisfactory deductions from the experience obtained in the treatment of tetanus by wounds inflicted in war where the element of infection, surgical treatment, and after care play such a vital part. Therefore it seems that more logical deductions can be obtained from observation of cases of tetanus occurring in civil life. The nature of the remedial agents employed may also vary greatly, particularly as regards the strength of the antitoxin. In this country we shall soon have a pretty definite standard, thanks to the extraordinarily efficient and intelligent work of standardization of such agents by the United States Public Health Service and the increasing facilities for obtaining reliable preparations of antitoxin manufactured by State and municipal authorities in conformity with such standards. It has been shown by a number of observers that many preparations of tetanus antitoxin, especially those made abroad, vary tremendously in their strength and composition, and it would be manifestly impossible for a foreigner to utilize the recommendations contained in this paper without comparing the relative strength of the preparations at his disposal.

The Standard of Mortality. Broadly speaking, we ought to be able to establish two periods for our observations; one before the introduction of any so-called specific treatment, the treatment then being limited to the administration of a sedative whose necessity has always been recognized. We have two important statistics covering that era in the mortality of tetanus; during the Civil War 89.3 per cent. and the Franco-Prussian War 90 per cent. These observations, however, fall within the preantiseptic era. The paper of Ashhurst and John[2] (which contains the most satisfactory and intelligent exposition of the subject up to date) gives a series of 435 cases from 1897 to 1911, contributed by thirteen authors, with a mortality of 66 per cent. Another and most important factor is the promptness with which treatment is begun. It is my belief, though quite impossible to state it statistically, that this element is a most

[2] Am. Jour. Med. Sci., June, 1913.

important factor, and I recommend breaking all speed laws to carry it out. We should be fully as prompt as in the treatment of an acute perforation of the gastro-intestinal tract. In a small proportion of cases it may be possible to recognize preliminary manifestations before the disease asserts itself in its classical manifestations. Localized cramps or twitching of the extremities may be recognized if anticipated. In 20 per cent. of cases it is stated that trismus is not the first symptom. The recognition of tetanus bacilli in the wound and the possible development of diagnostic serum reactions should be of assistance.

Choice of Treatment. The number of remedial measures suggested is almost infinite. Three stand out today from all others, namely, antitoxin, magnesium sulphate, and carbolic acid. Only these three will receive here any serious consideration.

It may be interesting to study the various forms of treatment now being used in the European war, although a study of results will have to be deferred till accurate reports can be collected.

Treatment of Tetanus in the Present European War. One obtains the impression that at present (1916) the amount of tetanus is not very great, notwithstanding that the trench fighting and the severe cold with its consequent frost-bites would favor its development. There appears to have been a good deal of tetanus in the early conflict, but the increasing prophylactic treatment with antitoxin now seems to be keeping it in check.

One finds as much diversity in the treatment of tetanus in military life as in civil, and the customs seem to vary largely in the various countries.

Treatment of Tetanus in England. The most satisfactory exposition of the treatment is contained in a little booklet *Memorandum on the Treatment of Injuries in War, Based on Experience of the Present Campaign*, July, 1915, published by the Royal Army Medical Corps. It is given in full, as it seems to be the best single comment on the methods available. It will be noted that the administration of tetanus antitoxin, and particularly the intraspinal method, is the method of choice:

"Tetanus. The heavily manured soil of the districts in which fighting has occurred frequently contains the spores of tetanus bacilli; these, in many wounds, are driven deep into the tissues and may find there the anaërobic conditions suitable for their development. Should the bacilli establish themselves in such a wound they give rise to toxins which have a great affinity for nervous tissues and produce the well-known symptoms of the disease.

"Prevention. A. *General Measures.* The steps advocated in other parts of this pamphlet for the cleaning, dressing and drainage of freshly received wounds, as well as for their appropriate surgical treatment, with a view to minimizing the risks of sepsis, are those which, if fully carried out, will also minimize the risk of tetanus. They need not, therefore, be further described here.

"B. *Special Measures.* These resolve themselves into the prophylactic use of tetanus antitoxin, a proceeding of well-established value.

"*Prophylactic Use of Tetanus Antitoxin.* Since in the first two months of the war more cases of tetanus occurred than had been anticipated, either by ourselves or our Allies, it was decided to direct that a preventive dose of serum should be given to every wounded man in place of leaving this, as had been done at first, to the discretion of the medical officer. The results have been excellent, and, in the last six months, there have only been 36 cases of the disease among those who received a preventive dose of serum within twenty-four hours of being wounded. That this is not due to the possible absence of the cause of infection from the soil is clear from the following facts: (1) Bacteriological examination of the wounds has often proved the presence of tetanus bacilli, although no tetanic symptoms have followed. (2) Many instances of slight trismus, or of localized tetanic spasms of a muscle or a group of muscles, have been reported, without the subsequent development of generalized tetanus. (3) Thirty-four cases of severe tetanus have been reported in this period among the very small fraction of wounded men who, for one reason or another, had not received a preventive dose of the serum within twenty-four hours. (4) A considerable number of wounded horses continue to develop the disease.

"The general use of preventive inoculation of the serum has also had an effect on the severity of the symptoms if, in spite of the preventive dose, the disease should subsequently develop. For example, of the 34 cases mentioned above, which did not have a preventive dose within twenty-four hours, 32 died, a case mortality of 94.1 per cent.; whereas of the 36 cases which occurred among the enormously larger class of wounded who *had* received a preventive dose, 28 died, a case mortality of 77.7 per cent.

"The preventive dose of 500 units should be given subcutaneously at a distance from the wound at the earliest possible moment, and the fact of inoculation, as well as the size of the dose, should invariably be recorded on the 'tally.' In severe wounds medical officers not infrequently give 1500 units; there is no objection to this, but at the same time there is no evidence that the smaller dose is insufficient if given promptly.

"It should be remembered that injuries other than those caused by bullets or shells may also become infected; several fatal cases have followed trivial injuries, for which the soldier did not report sick at the time, and others have followed on the gangrene due to frost-bite. It would be wise to give a preventive dose in all instances in which the danger of infection of a wound with contaminated soil may be presumed to exist.

"Several different preparations of tetanus antitoxin are in use. These have all been recently tested, and in each case they were found to contain at least the number of units claimed.

"(The question of Anaphylaxis is dealt with below.)

"*Influence of the Duration of the Incubation Period on the Severity of the Attack.* The general experience has been, as was to be expected, that the shorter the interval between the receipt of the wound and the appearance of the symptoms the smaller the chance of recovery. At the same time, cases have recovered in which the symptoms appeared six days after the wound, and cases have proved fatal where nineteen days had elapsed. The average incubation period of 43 fatal cases was 8.83 days, and that of 26 cases which recovered 11.57 days.

"TREATMENT WHEN THE DISEASE IS ESTABLISHED. A careful study has been made of 179 cases in which certain particulars which had been called for were furnished. Of these 179 cases, 140 have died, a case mortality of 78.2 per cent. Although this figure is disappointingly high, it must not be forgotten that the majority of these cases were also suffering from severe forms of sepsis, and in a considerable number of them the reporting officer stated that the tetanic symptoms had completely subsided under treatment, the patient dying from septicemia, gangrene, secondary hemorrhage, or other causes.

"A. *Local and Surgical Measures.* Steps should be taken to open up and clean the wound, if this has not already been done, and the freest possible drainage should be secured. The local application of strong antiseptics, swabbing with pure carbolic acid, the free use of hydrogen peroxide, and similar measures, have been tried, but appear to have had little influence on the course of the disease. Surgical interference of a grave nature, such as amputation of a limb, has been carried out in a number of instances; but such cases have almost always died, though not necessarily from the severity of the tetanic symptoms.

"B. *General Measures.* The patient should be kept in a perfectly quiet and darkened room, maintained, as far as possible, at an equable temperature. The avoidance of all external stimuli, likely to start a spasm, is to be aimed at, and some have advocated the bandaging of the eyes, the plugging of the ears with wool, the placing of the feet of the bed on rubber disks, etc., with this object in view. It is of great importance to maintain the strength of the patient by means of adequate fluid nourishment, given in small quantities at frequent intervals, and by the rectum if swallowing tends to induce spasm.

"C. *Use of Anesthetics and Sedatives.* As regards the former, chloroform is most commonly used, though ether has been preferred by some, especially when required for a small operation or for the dressing of a painful wound. Their value is well recognized. As

sedatives, chloral hydrate, potassium bromide, and morphin are most frequently used for the purpose of controlling spasm, the first named being the most valuable. They are of undoubted value in this direction, but do not appear to modify the course of the disease to any great extent. Too frequent or too large doses may do harm. Chloretone, in doses of 30 to 40 grains in olive oil, given by the rectum, has been well spoken of for the same purpose of controlling spasm.

"D. *Carbolic Acid Method.* This has been given a trial in a considerable number of cases, usually in combination with tetanus antitoxin, but the results have been disappointing. The dosage must be considerable and the treatment must be kept up well into convalescence; in one case a relapse was reported to have followed its abrupt discontinuance. The following strengths of carbolic acid have been recommended:

I. 20 c.c. doses of a 1 per cent. solution.
II. 20 minim doses of a 2 per cent. solution.
III. 2 c.c. doses of a 5 per cent. solution.

"The inoculations are made either subcutaneously or intramuscularly every three or four hours, the interval between the doses being lengthened as the spasms diminish in frequency. In no case has any local trouble been reported, nor has carboluria followed even large and frequently repeated doses.

"E. *Magnesium Sulphate.* Three methods of employing this drug have been advocated: (*a*) The subcutaneous inoculation of doses of 2 c.c. of a 25 per cent. solution. (*b*) The subcutaneous inoculation of large quantities of a more diluted solution, Greely recommending the injection of a 1 to 2 per cent. solution in quantities varying from 1 pint to 1 quart every three hours, according to the severity of the case. (*c*) The intrathecal method. For this Philips advises the inoculation of a 25 per cent. solution, after withdrawing some of the cerebrospinal fluid, 1 c.c. being given for each 25 pounds of body weight, corresponding to 5 or 6 c.c. for a man of average size. The head of the bed should be propped up after the operation. The advocates of this method claim that it gives relief from pain, controls spasm, and ensures sleep. It has been used in this war chiefly by the intrathecal method, but, like carbolic acid, has not proved reliable.

"F. *Tetanus Antitoxin.* This is the only treatment as to the employment of which there has been anything like general agreement. It has been used in one form or another in almost every case, and when cure has resulted it has commonly been given the credit. Whatever method be employed it is clear that three general principles must be observed to obtain the best results: (1) It must be employed at the earliest moment possible; a dose of 1000 to 1500 units given at a time when there is little more than a fear that tetanus may develop, may influence the course of the

disease favorably. (2) It must be given in large doses, and these should be frequently repeated until the symptoms show definite signs of amelioration. (3) It must be kept up, although in smaller and less frequent doses, well into convalescence, in order to obviate the tendency to relapse.

"The most favorable results appear to have been obtained by the employment, in the first instance, of the intrathecal combined with the intravenous methods, the subcutaneous method being used to reinforce the others in the succeeding days or to replace them as the symptoms diminish in intensity.

"*Dosage.* An initial intrathecal dose of 3000 units followed by the intravenous injection of doses ranging between 5000 and 20,000 units, according to the severity of the symptoms, has been reported in many instances to have had a favorable effect. In severe cases the intrathecal dose of 3000 units may be repeated the next day. The subsequent indications as to dosage depend upon the progress of the case; if this is favorable the above methods may be supplemented or replaced by the subcutaneous one, doses of from 5000 to 10,000 units being given every day or every second day.

"*Anaphylaxis.* Symptoms of this grave condition are well known in animals to follow the administration of a second dose of the same serum when the lapse of time between the two doses exceeds ten or twelve days. There was some reason to fear its occurrence in men who had received a preventive dose of tetanus serum after being wounded, and who, on account of the development of the disease after an interval of twelve days or more, were given therapeutic doses of the same serum. Again, a large number of men who have returned to the front after recovery from a wound are again wounded, and the question has been raised as to the possible danger of giving another preventive dose of serum after an interval of some weeks or months. It is, however, well known that man is much less sensitive to anaphylaxis than the guinea-pig and the rabbit, and this has been fully borne out by the experience of the war. In spite of close inquiries on the subject no certain instance of true anaphylaxis has been recorded. The few cases which have been mentioned in reports have, on investigation, turned out to be instances of serum sickness and to have had no grave results. It does not, therefore, appear to be justifiable to withhold the serum in the case of a man wounded for the second time; at all events, it appears better to run the small and chiefly theoretical danger of anaphylaxis than the very grave one of tetanus.

"In cases in which there is reason to fear the occurrence of anaphylactic shock, various procedures have been recommended to lessen the danger. The majority of these are "fractional" methods of administering the serum, a preliminary inoculation of 2 or 3 drops of the serum being given, in dilution, followed in five minutes by a dose of 0.5 c.c. If no untoward symptoms result it is said

that the full dose may safely be inoculated ten minutes later. A similar fractional method has been advised if the intrathecal methods are selected, but there has been no opportunity of judging of their value. Administration of the serum under chloroform anesthesia is also said to lessen the danger. If symptoms of shock should develop in spite of these precautions, adrenalin has been stated to be useful, given intravenously in high dilution if the symptoms are urgent, hypodermically in less urgent condition in doses of a few minims of a 1 to 1000 solution."

Treatment of Tetanus in Italy. Dr. Carlo Savini, of New York City, who has recently returned from the Italian war zone, writes under date of October 22, 1915, as follows:

"The consensus of opinion in Italy seems to be very favorable to the Bacelli treatment of tetanus. It is claimed to give only 17 per cent. mortality, while the symptomatic (or expectant) and the antitetanic serum treatment give from 50 per cent. to 78 per cent. mortality.

In the war zone the prophylactic injection of antitetanic serum is compulsory for all the wounded, and I was told that very few cases of tetanus are found.

The treatment of tetanus is left to the judgment of each doctor, and it is not possible now to state how often the Bacelli treatment is being used and what the results are.

In conclusion, in Italy everybody agrees in the prophylactic value of the serum. In the therapy of tetanus the treatment of Bacelli seems to be the most favored; next is the treatment with injection of magnesium sulphate solution, and last the treatment with antitetanic serum."

Professor R. Bastianelli writes under date of December 12, 1915:

"I am not able to answer satisfactorily your question about the treatment of tetanus in Italy. The present war has given ample occasion to collect experience on that argument, but the results are not yet tabulated. Prior to the war, Bacelli's method was used extensively by us and the reports have been satisfactory. It is possible, however, that many unfavorable cases have not been reported. The antitoxic method, either with Tizzoni's antitoxin or with Behring's serum, has been employed extensively, and so far as I know with rather good results in cases with late onset and slow course, while in the so-called acute cases the results have been very poor and in my experience constantly bad. I have used the serum intravenously and intraspinally at the same time, giving also large doses of chloral and intramuscular injections of magnesium sulphate."

Treatment of Tetanus in France. In France there is also no distinct line of treatment. October 11, 1915, Dr. Charles Walther writes me:

"I find it difficult to give you exact information, as I doubt

if there is a single method of treatment of tetanus which is generally accepted. In addition to the classical treatment by heat, dark room, administration of chloral, I find there is a tendency to employ more and more antitetanic serum in large doses, 40 to 50 to 60 cm. daily subcutaneously or intravenously. Intraspinal injections in considerable amounts, between 40 and 60 c.c., every second day, with head and trunk lowered, seem to have given good results. Personally, I have had a certain number of successes in the intravenous and subcutaneous injections of antitoxin in large amounts, particularly of peripharyngeal injections in the subhyoid region at the base of the tongue.

"I believe I was the first, fourteen years ago, to make intraspinal injection of antitetanus serum in a case at the La Pitié Hospital. I have personally no experience in the use of magnesium sulphate or carbolic acid."

Treatment of Tetanus in Belgium. The treatment most favored by Dr. Depage when I saw him in February, 1915, was the antitetanus toxin, but I do not think he ever used it intraspinally.

I have not heard directly from the other fronts and can only surmise as to the methods employed. Stolbnyak states, in the *Russkiy Vrach*, Petrograd, summarized in the *Journal of the American Medical Association*, January 15, 1916, page 232:

"The best symptomatic results were obtained with chloral hydrate, from 1 to 7 gms. daily given by the mouth or rectum. For spasmodic contracture of the intestines and bladder hypodermic injection of from 0.5 to 1 gm. of a pituitary extract gave good results. Warm baths at 100° F. also proved effectual in symptomatic treatment. No benefit could be detected from treatment with antitetanus serum, intravenous or intraspinal; from 3 per cent. phenol solution; suspensions of pigs' brains; calcium lactate three times daily in doses of 30 drops of a 10 per cent. solution, or from magnesium sulphate in hypodermic injections of from 2 to 14 c.c. of a 25 per cent. solution, or by intraspinal injection of 15 c.c. of a 10 per cent. solution."

In Germany the treatment seems to be most varied, and includes a number of methods which would seem to have little but their novelty to recommend them. Violet light, salvarsan, ascitic fluid from cured patients, emulsion of pigs' brains, intravenous injections of ether, etc.

The method which seems to be most in favor is the magnesium sulphate treatment, particularly when injected into the spinal canal. Kocher's favorable report on its use seems to be responsible for its popularity.

Comparative Claims of Antitoxin Treatment, Magnesium Sulphate and Carbolic Acid. As has been stated before, it seems quite impossible at present to establish anything like a

statistical investigation with any hope of accurate results. Only if very large groups treated under similar conditions should show marked discrepancy in results would it be safe to draw any deductions.

THE ANTITOXIN TREATMENT. The antitoxin treatment may be divided into (*a*) subcutaneous administration, (*b*) intravenous, (*c*) intraspinal, (*d*) intraneural, (*e*) intracerebral. The last method we can dismiss, as it is no longer employed, and gave very bad results; the other methods promise better.

(*a*) The subcutaneous method, it is believed, lacks efficiency and should be used only as an adjuvant to the other methods.

(*b*) The intravenous administration is a distinct advance as regards efficiency and rapidity of results. My belief is, however, that it should be considered as an accessory rather than the main line of treatment.

(*c*) The intraspinal method appeals to me as complying most with the indications, namely, locating the antitoxin most directly to the lesion itself. Ashhurst and John have presented conclusively the evidence that the toxin of tetanus reaches the spinal cord by the peripheral nerves. They state that "the nearer the toxin gets to the spinal cord the more impregnably intrenched does it become in the nerve tissue."

It is not easy to determine who was the first responsible for the idea of injecting the antitoxin intraspinally. I find no mention of it prior to Schultze's article in the *Grenzgebiete der Medizin und Chirurgie*.

Personally, I have been much impressed with the evidence furnished by the experimental work and clinical results of Dr. W. H. Park and Dr. M. Nicoll, Jr., from the laboratory of the New York City Board of Health. I may state that in all my successful cases here reported the treatment has been conducted entirely on the lines laid down by these gentlemen and with their advice and coöperation. In the *Journal of the American Medical Association*, June 12, 1915, Nicoll reports 20 cases treated with the chief reliance on intraspinal injections, with 4 deaths. These cases represent an average severity, were under the care of different physicians and under varying conditions.

They recommend (1) from 3000 to 5000 units in the lumbar region of the spinal canal, preferably under an anesthetic,[3] the volume of fluid injected being brought up to 10 or 15 c.c. by the addition of sterile or normal saline, the exact amount being regulated to the age of the patient and the amount of spinal fluid withdrawn; (2) 10,000 intravenously at the same time; (3) repetition

[3] This recommendation of the author, I think, will be only exceptionally necessary, *e. g.*, in the case of children. It is important to remember this fact as the recommendation to *give* an anesthetic might deter some from utilizing this valuable method.—C. L. G.

of the intraspinal dose in twenty-four hours; (4) subcutaneous dose of 10,000 units three or four days later.

The above directions may suffice in a case of ordinary severity, but we believe that many cases will have to receive more antitoxin intraspinally than the two injections recommended and a good deal more intravenously. Case VIII received 6 injections, 29,000 units of antitoxin intraspinally and antitoxin in other forms up to 169,000 units.

I am inclined to think that in the future we shall use greater amounts of antitoxin intraspinally and especially in the initial dose. Dr. Boyd, of Springfield, recently reported a case of a young child in which treatment was begun at the end of a week, the child being then apparently moribund. Under an initial dose of 15,000 units intraspinally the patient made a prompt response and good recovery. I am inclined to think that in future cases of great severity I shall also begin with as large or possibly even larger dose.

In a mild case some question may arise as to whether more than the initial intraspinal dose should be administered. If improvement becomes manifest at once the second intraspinal dose may be well withheld, but the antitoxin intravenously should be administered daily until the improvement is certain. A guide to the necessity for antitoxin treatment may be had in estimating the antitoxic contents of the blood. This procedure, however, requires the coöperation of an expert worker, and is time-consuming and not really necessary. There is probably very little danger in overdoing the dosage so long as active symptoms of tetanus are present. The fluid withdrawn from the spinal canal after the preliminary injection of antitoxin has a milky tinge, but was found in our cases to be quite sterile.

(*d*) If we accept the value of the intraspinal injection of antitoxin there seems to be little call for intraneural injections which some fifteen years ago were extensively employed and apparently with an improvement over the then commonly used methods. Unless better evidence can be furnished of the value of intraneural injections they can be eliminated, for they require the performance of a formal operation under an anesthetic which in the patient's grave condition is inadvisable, besides being a more formidable procedure than the simple injection intraspinally. If we accept the doctrine that the intraneural injection is superfluous we can also apply this dictum to the amputation of an extremity.

Magnesium Sulphate. This treatment was originated in the United States by Meltzer and Auer. In the *Journal of the American Medical Association*, March 25, 1916, Meltzer writes of the "Inhibitory Properties of Magnesium Sulphate and their Therapeutic Application in Tetanus." He says:

"The action may appear to some as merely a symptomatic

one; it relieves the convulsion. But even if this would be indeed its only favorable effect, it would be of inestimable value, since the suffering in tetanus and the fatal outcome of this horrible disease is nearly exclusively due to the consequences of the tetanic symptoms. And I may assert that no other remedy is capable of relieving the furious symptoms to such a satisfactory degree as do the injections of magnesium sulphate."

Magnesium sulphate can be administered intraspinally, subcutaneously, intravenously, intramuscularly plus ether inhalation. Meltzer summarizes the treatment as follows:

"The best general plan for treatment of tetanus would seem to be as follows:

"In each and every case of tetanus, 1.2 c.c. of a 25 per cent. solution of magnesium sulphate should be given by subcutaneous injection three or four times a day throughout the entire disease.

"When the disease is complicated by severe tetanic attacks, 1 c.c. of a 25 per cent. solution for every 10 kg. (20 pounds) body weight (in adults) should be given by the intraspinal method.

"When the disease is attended by immediately dangerous tetanic complications, from 2 to 3 c.c. per minute of a 6 per cent. solution of magnesium salts should be given then by an intravenous injection until dangerous symptoms subside or the respiration becomes shallow or too slow.

"When the respiration seems to become impaired in consequence of the administration of magnesium salt by the intravenous, intramuscular, or subcutaneous methods, calcium chloride should be injected in the manner described above.

"It is advisable to have at hand an apparatus of intrapharyngeal insufflation ready for use whenever the respiration becomes slow or shallow.

"Finally the simultaneous treatment by antitetanic serum should not be neglected."

No statistics are given in support of the success of this method of treatment. Reference is made to a favorable report by Kocher.

This treatment was employed at the time of its development in New York City; but the general impression is that it has too many dangers and drawbacks *per se*, particularly in paralyzing the respiration. Its intraspinal administration undoubtedly checks the convulsions more speedily than any other method. I should prefer however, to substitute for it the inhalation of a general anesthetic to a very slight degree as used to be done fifty years ago.

The method was employed quite a little following Meltzer and Auer's original description. Of late there seems to have been little attempt to use it in America, but in the present war it seems to stand out as prominently as any one method in Germany and to some extent in other countries.

Cloetta[4] warns against the use of magnesium sulphate and notes its resemblance to the action of curare which was used in tetanus fifty years ago.

Carbolic Acid Treatment. This treatment was initiated by Bacelli, according to Ashhurst and John, in 1888. The mortality claimed for it is the lowest of all, 17 per cent. It seems remarkable that it has not come into more general use especially in America. It is administered, according to Ashhurst and John, 1 c.c., 1 per cent. solution, every few hours, perferably into the muscles along the spine, until 80 or 100 centigrams are given in twenty-four hours.

Sainton[5] reports 22 cases of tetanus treated in the French Army Hospitals by the Bacelli method, with 16 deaths. This is not a very favorable showing for the method, but it must be remembered the difficulties of estimating the results of subjects wounded and treated under war conditions.

Summary of Proposed Choice of Treatment. As I have stated before, it is presumed that the wound treatment will be that suitable to the injury and particularly to the most efficient form of drainage and liberation of sloughs, removal of foreign bodies, etc., that may harbor tetanus germs or favor their development. I doubt if today we are justified in performing an amputation for the relief of tetanic manifestations as in the intraspinal administration we have gone a step further in efficiency. Likewise, I will omit the questions of nursing and the use of sedatives. One sedative, however, should be alluded to as it has been thought to have curative qualities *per se*, namely the chloretone treatment advocated by Hutchings.[6]

I should also be inclined to make a trial of atropin as a method of controlling spasm, as this drug has lately impressed me greatly in the treatment of spasmodic contraction of the pylorus.

Antitoxin treatment should be begun immediately on suspicion of tetanus developing rather than waiting for the classical symptoms. If this principle is firmly established, I believe we shall have done much to lessen the dangers of the disease. Antitoxin should be given at once, first into the wound or region of the wound, say 1500 units, intraspinally, without an anesthetic, unless the treatment of the wound calls for the administration of a general anesthetic, 5000 to 20,000 units. In the course of the first twenty-four hours, in addition to the above, 10,000 to 20,000 units should be administered intravenously in divided doses, say two or three. Antitoxin intravenously from 5000 to 15,000 units should be given next day no matter whether the symptoms remit or increase. On the third day if, notwithstanding the treatment, the patient's symptoms continue very severe or appear worse the intraspinal

[4] Correnspondenz-Blatt f. schweizer Aerzte, 1915, No. 3.
[5] Journal de Chirurgie, September, 1915.
[6] Annals of Surgery, vol. l.

treatment should be repeated. The intraspinal, of course, gives temporary increase of symptoms and steep elevation of temperature but this fact need not of itself cause alarm. If after this treatment the patient holds his own or improves the intraspinal need not be repeated but the daily injection of antitoxin intravenously should be given until obvious remission or cure results.

The severity of the cases will, of course, vary and the resulting treatment will depend on this factor. Attention is called to Case VIII, who received a total of 169,000 units, which included 29,000 units given intraspinally in six sessions, in this case, daily, although I doubt if this frequency is often indicated.

The series of cases I have reported is, of course, small, and I am fully aware of the dangers of deducing results from such small material. On the other hand, I have the impression, though I find it hard to put into words, that, although many of these cases were of the severest type and very ill, we had, particularly in the intraspinal method, complete control of the situation. With this feeling of confidence, therefore, I should hesitate to offer any other method of treatment until there is better evidence of the superiority of these other methods.

THE PATHOLOGIC CHANGES IN THE SYMPATHETIC SYSTEM IN GOITER.*

By Louis B. Wilson, M.D.,
ROCHESTER, MINNESOTA.

The amount and character of the pathologic changes in the sympathetic ganglia removed at operation or at autopsy from patients with exophthalmic goiter have been studied by other observers, meagerly and rarely by modern methods. I have reviewed elsewhere[1] the literature of previous reports. So far as the findings have been positive, they have shown that in exophthalmic goiter the cells of the sympathetic ganglia exhibit various stages of degeneration. The paucity and incompleteness of the reported observations, however, together with Cannon's[2] recent experimental production of some of the symptoms of exophthalmic goiter in cats by constant stimulation of the thyroid through the sympathetic system, have warranted a more careful study of the material accumulating in the Mayo Clinic.

* Read before the Association of American Physicians, Washington, D. C., May 10, 1916.

Previous Report in the Present Series of Observations.

Durante and I[1] have recently reported our observations on twenty superior cervical sympathetic ganglia removed at operation from sixteen patients with hyperplastic toxic (exophthalmic) goiter. Our findings may be briefly summarized as follows:

1. Definite histologic changes in the cells of the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goiter occurred in all cases examined.

2. These histologic changes consisted of various stages of degeneration, namely (*a*) hyperchromatization, (*b*) hyperpigmentation, (*c*) chromatolysis, and (*d*) atrophy or (*e*) granular degeneration of the nerve cells.

3. Some of the ganglia contained cells resembling the partially differentiated cells found in the ganglia of infants.

4. Accompanying the more advanced changes in the ganglion cells were similar degenerative changes in the nerve fibers and an increase of connective tissue throughout the ganglion, but especially in the outer and middle coats of the vessels and in the periganglionic tissue.

5. So far as could be determined from the small number of observations, the pathologic changes in the cervical sympathetic ganglia were parallel to the stage and intensity of the symptoms of hyperthyroidism and to the hyperplastic and regressive changes in the thyroid.

Material for the Present Study.

The present report is based on a study of the cervical and other sympathetic ganglia removed at autopsy from twelve patients dying during the course of exophthalmic goiter. The observations have been controlled by similar studies on sympathetic ganglia removed at autopsy from nine patients dying of diseases other than exophthalmic goiter, and by studies on gasserian ganglia removed at operation from six patients with trifacial neuralgia.

All ganglia removed at operation were fixed within five minutes after removal, and the material from autopsies was fixed within three hours after death. Some portions of ganglia were examined in frozen sections of the fresh tissue. The remainder of the specimen or specimens was fixed in 10 per cent. formalin. Selected blocks were cut frozen without embedding and the sections stained with Sudan III or by Nissl's method. Other blocks were embedded in paraffin and cut in serial sections, which were stained with hematoxylin-eosin, by Weigert-van Geison's method for connective tissue, by Weigert-Luden's method for myelin,[3] and by Held-Nissl's method for distribution of chromatin. Other blocks were used for silver impregnation by Ramon y Cajal's,[4] Levaditi's,[5] or Bielschowsky's methods. Others were fixed and stained by

Bensley's[6] acetic-osmic-bichromate method for mitochondria. The most satisfactory results were obtained by the use of Sudan III, Held-Nissl's, Ramon y Cajal's, and Bensley's stains.

Protocols.

Case 1 (A156,845).—The patient was a female, nineteen years of age, who had had severe symptoms of hyperplastic toxic goiter for five months. Recently the thyroid had enlarged very rapidly. The patient died of hyperthyroidism a few days after coming to the Clinic, without having been operated on. At autopsy, three hours and forty minutes after death, there was found marked hyperplasia of the thyroid, marked exophthalmos, symmetrical brown pigmentation of the conjunctivæ, marked emaciation, petechial hemorrhages in the skin, in the parietal peritoneum of the true pelvis, and elsewhere in the pelvic organs, marked hypertrophy of the myocardium of the left ventricle, slight nodular sclerosis of the coronary arteries, and fatty changes in the intima. The thymus weighed 80 grams.

Microscopically, the thyroid showed progressive advanced hypertrophy and hyperplasia, Type B[7]. The superior cervical ganglia showed very marked hyperpigmentation and extensive granular degeneration of the cells, many of which were atrophic or consisted of only small masses of pigment.

Case 2 (A153,535).—The patient was a female, nineteen years of age; for five months had shown symptoms of severe exophthalmic goiter. The systolic blood-pressure was 180, diastolic 75, pulse-rate 150 to 168. After two weeks' preparation the left superior thyroid vessels were ligated. The temperature remained normal and the pulse fluctuated from 100 to 118. Death occurred three days after operation. The macroscopic findings at autopsy, made three hours and fifteen minutes after death, were those of severe exophthalmic goiter.

Microscopically, the thyroid showed progressive advanced hypertrophy and hyperplasia, Type B[7]. Many of the cells from the cervical sympathetic ganglia were in the state of advanced degeneration noted in Case 1, though not nearly so many cells were affected (Fig. 1).

Case 3 (A144,809).—A female, thirty years of age; had had severe symptoms of exophthalmic goiter for eight months. At the time of examination the systolic blood-pressure was 165, diastolic 70, and pulse-rate 128. The left superior thyroid vessels were ligated, and four months later the right superior thyroid vessels were also ligated. Two weeks after the second ligation the right lobe, isthmus, and pyramidal lobe of the thyroid were extirpated. Death occurred the following day. At autopsy, two hours and thirty minutes after

death, an advanced chronic myocarditis with fatty degeneration and advanced degenerative changes in the liver and kidneys were found.

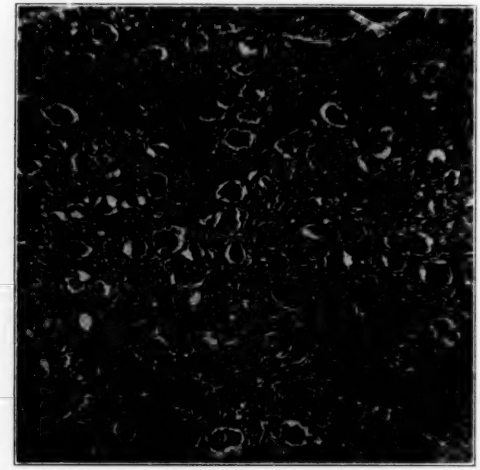

FIG. 1 (Case 2).—Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns, × 120 diameters. Advanced degeneration of many cells.

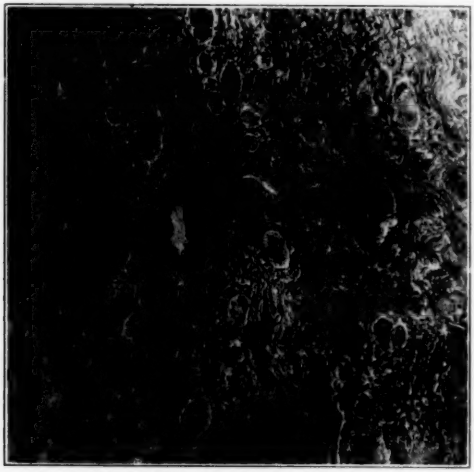

FIG. 2 (Case 3).—Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns, × 120 diameters. A few normal cells, many showing advanced degeneration.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C–1[7]. In the cervical sym-

pathetic ganglia a few cells were apparently normal. Many showed varying degrees of hyperpigmentation and granular degeneration (Fig. 2).

CASE 4 (A136,418).—The patient, a female, twenty-five years of age, had shown symptoms of exophthalmic goiter for two years, with marked increase in severity during the last three weeks. At the time of examination the systolic blood-pressure was 145, and diastolic 80. The left superior thyroid vessels were ligated, and five days later the right superior vessels were ligated also. Four and a half months later the right lobe, isthmus, and a small portion of the left lobe of the thyroid were resected. The patient died nine days after the operation. At autopsy, eight hours after death,

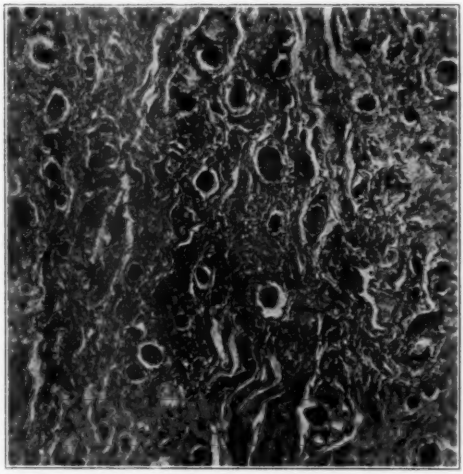

FIG 3 (Case 4).—Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns, × 120 diamters. A few normal cells, many in varying stages of degeneration.

the macroscopic findings were a hypertrophied thymus, acute myocardial degeneration, and dilatation of the heart, congestion and degeneration of all parenchymatous organs, and severe purulent bronchitis. The cervical sympathetic ganglia were noticeably enlarged.

Microscopically, the thyroid showed early regressive advanced parenchymatous hypertrophy and hyperplasia, Type C–1[7]. The ganglia showed a few fairly normal cells, but many others in varying stages of degeneration (Fig. 3).

CASE 5 (A11,264).—This patient was a female, thirty-three years of age, who had had symptoms of exophthalmic goiter beginning two years and five months previously. At the time of examina-

tion the systolic blood-pressure was 138, diastolic 90, and pulse-rate 138. The left superior thyroid vessels were ligated, and two weeks later the right superior thyroid vessels were ligated. Two and three months after the last ligation, hot-water injections were made into each lobe of the thyroid, and three weeks after this, or four and a half months after the first ligation, the right lobe and isthmus of the thyroid were extirpated. The patient's pulse-rate increased to 140, and she died twenty-four hours after the operation. At autopsy, two hours and thirty minutes after death, the principal macroscopic findings were acute and chronic myocardial degeneration, with a dilated heart, general parenchymatous degeneration not so severe as usual in exophthalmic goiter, and chronic nephritis.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C–1[7]. A few cells in the cervical sympathetic ganglia were normal. Many showed varying degrees of hyperpigmentation and granular degeneration.

Case 6 (A149,095).—The patient, a female, twenty-eight years of age, had shown symptoms of exophthalmic goiter for six years, with a maximum severity within the first year. At the time of examination she had slight exophthalmos, a systolic blood-pressure of 150, a diastolic of 80, and a pulse-rate of 120. The left superior thyroid vessels were ligated, and two weeks later hot-water injections were made into the right lobe of the thyroid. One week after this the right superior thyroid vessels were divided and the ends ligated separately. Two weeks after the last operation the patient died. At autopsy, one hour after death, the principal macroscopic findings were bilateral lobar pneumonia with infarction of right upper lobe and hypertrophy and dilatation of the heart.

Microscopically, the thyroid showed a regressing advanced hypertrophy and hyperplasia, Type C–2[7]. The cervical sympathetic ganglia showed many cells apparently normal, a few in advanced stages of degeneration, and a very few in intermediate stages of degeneration.

Case 7 (A-135,172).—The patient, a female, twenty-nine years of age, had had goiter for sixteen years, with moderate symptoms of thyrotoxicosis for twelve years, the maximum severity of toxic symptoms having been attained about four years ago, since which time there had been some abatement. At the time of examination the systolic blood-pressure was 175, the diastolic 78, and the pulse-rate 114. The left and right superior thyroid vessels were ligated, and four months later the right lobe, isthmus, and a small piece of the left lobe of the thyroid were extirpated. The patient died one week after operation. At autopsy, two hours after death, the macroscopic findings were an hypertrophied thymus, bilateral emphysema, acute splenitis, and chronic nephritis, with congestion.

Microscopically, the thyroid showed advanced regressive changes on chronic hypertrophy and hyperplasia, Type C–2[7]. The superior

cervical sympathetic ganglia showed many cells apparently normal and a few in advanced stages of degeneration. The total number of cells was apparently much reduced (Fig. 4).

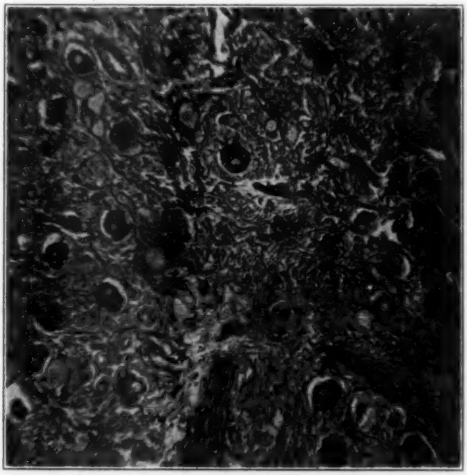

FIG. 4 (Case 7).—Section of right superior cervical sympathetic ganglion, silver impregnation, 5 microns, × 120 diameters. Marked reduction in the number of cells, many apparently normal, and a few in advanced stages of degeneration.

CASE 8 (A109,170).—This patient, a female, forty-seven years of age, had noticed enlargement of the thyroid for four years, but symptoms ascribable to thyrotoxicosis began only one year prior to the enlargement. At the time of examination the systolic blood-pressure was 140, diastolic 45, and pulse-rate 120. The right and left superior thyroid vessels were ligated. The patient improved steadily in health for eight or nine months, and then began to lose appetite, weight, and strength. A year after the first operation, several hot-water injections into the thyroid were made. The general health improved, but there was a rise in blood-pressure to 166 systolic, 90 diastolic, and a rise in pulse-rate to 140, six months after the injections. One month later the pulse-rate was 176. Death occurred a month after this, or one year and eight months after the first operation,. At autopsy, three hours after death, the macroscopic findings were hypertrophy and dilatation of the heart, chronic cholecystitis, and parenchymatous degeneration of all organs.

Microscopically, the thyroid showed advanced regression on an old parenchymatous hypertrophy and hyperplasia, Type C–3[7]. The superior cervical sympathetic ganglia showed a great reduction in the total number of cells, many of the remaining ones of which,

however, were normal, while a few were in advanced stages of granular degeneration.

CASE 9 (A-147,479).—The patient, a female, forty-four years of age, had had thyroid enlargement for thirty-two years, with symptoms of thyrotoxicosis beginning five years ago and gradually increasing to the present time. At the time of examination the patient had lost weight from 150 to 114 pounds. The systolic blood-pressure was 122, diastolic 80, and the pulse-rate was 120. Patient died without operation. At autopsy, two hours and forty-five minutes after death, the macroscopic findings were a medium-sized retrotracheal thyroid, hemopericardium, and right hemothorax with adhesions, and acute parenchymatous degeneration

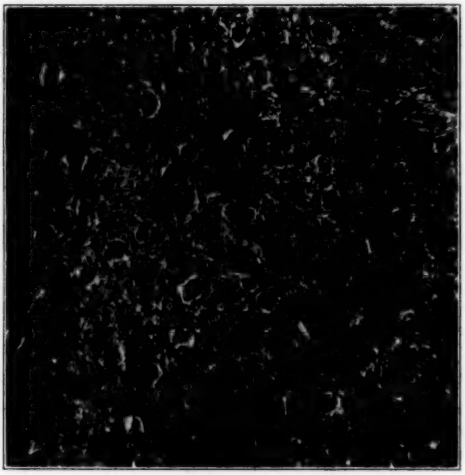

FIG. 5 (Case 9).—Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns, × 120 diameters. Many normal cells, many hyperpigmented, and a few in advanced stages of degeneration.

with fatty changes in the heart, liver, and kidneys, and chronic nephritis.

Microscopically, the thyroid showed advanced regression on chronic parenchymatous hypertrophy and hyperplasia, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Of those present, many were normal, and a few were in advanced stages of degeneration (Fig. 5).

CASE 10 (A67,759).—The patient, a female, fifty years of age, had had enlargement of the thyroid for twenty years, with mild symptoms of thyrotoxicosis beginning coincident with the thyroid enlargement and lasting for three years. Six months previous to examination, the symptoms of thyrotoxicosis returned. At the time

of examination, the patient was emaciated, the pulse-rate was 200, with a cardiac arrhythmia growing progressively worse. Death occurred three days after examination. At autopsy, one hour after death, the principal macroscopic findings were enlarged thyroid, myocarditis, atrophic and fatty changes in the liver, and chronic nephritis.

Microscopically, the thyroid showed advanced regressive changes in parenchymatous hypertrophy and hyperplasia with some adenomatosis, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Most of those present, however, were fairly normal while a few showed advanced degenerative changes.

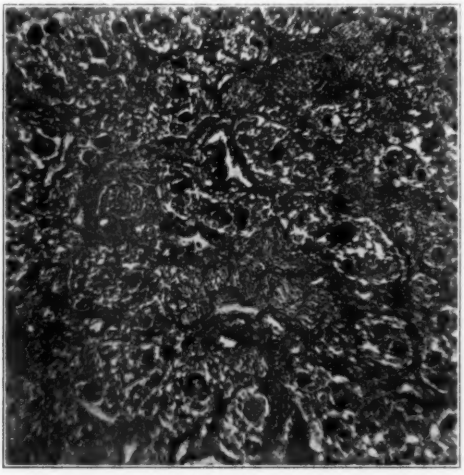

FIG. 6 (Case 11).—Section of left superior cervical sympathetic ganglion, silver impregnation, 10 microns, × 120 diameters. Marked reduction in the number of cells, many normal, and many in varying stages of advanced degeneration; marked increase of fibrous connective tissue.

CASE 11 (A156,404).—The patient, a female, fifty-five years of age, had had thyroid enlargement for twenty-four years. A thyroidectomy of the right lobe was done six years before, followed by a remission of all symptoms until a recent onset of cardiac distress. At the time of examination she had lost weight from 150 to 135 pounds; had a systolic blood-pressure of 158, and a diastolic of 88. The left lobe of the thyroid was extirpated and the internal jugular on the left side ligated. The patient died three days after operation. At autopsy, two hours and thirty minutes after death, the macroscopic findings were marked acute edema of the glottis, moderate hypertrophy of the myocardium of the left ventricle, marked disseminated nodular thickening of the aorta and of the aortic

and mitral valve leaflets, and a moderate sclerosis of the coronary arteries.

Microscopically, the thyroid showed advanced regression of a moderate hypertrophy and hyperplasia, with considerable adenomatosis, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Of the cells present, many were normal, but a large number were in varying stages of advanced regeneration. There was marked increase of fibrous connective-tissue in the ganglia (Fig. 6).

Summary of Protocols.

A study of the preceding protocols shows that of the 11 patients, 7 were females between nineteen and thirty-nine years of age and 4 were females between forty-eight and fifty-five years of age.

When considered in relation to the duration and stage of the symptoms of exophthalmic goiter the cases may be roughly grouped into three classes:

A. Cases still presenting active progressive symptoms of hyperplastic toxic (exophthalmic) goiter. These are as follows:

1. (A156,845) Female, aged nineteen years, symptoms five months, severity 3.*
2. (A153,535) Female, aged nineteen years, symptoms five months, severity 2 to 3.
3. (A136,418) Female, aged twenty-five years, symptoms two years, severity 3.
4. (A144,809) Female, aged thirty years, symptoms eight months, severity 3.

B. Cases in which the severity of the symptoms of hyperplastic toxic goiter had partially subsided, though the acute toxic condition was yet present. These are as follows:

5. (A11,264) Female, aged thirty-three years, symptoms two years, present severity 2.
6. (A149,095) Female, aged twenty-eight years, symptoms six years, severity 3.

C. Cases in which the acute toxic symptoms had almost, if not completely, subsided. These are as follows:

7. (A135,172) Female, aged thirty-nine years, goiter for sixteen years, maximum severity four years ago 3, present severity 1.
8. (A109,170) Female, aged forty-eight years, goiter four years, symptoms five years, present severity 1.
9. (A147,479) Female, aged forty-nine years, goiter thirty-two years, symptoms for two years, present severity 1 to 2.
10. (A67,759) Female, aged fifty years, goiter for twenty years, symptoms during first three years of goiter, then remission until during last six months, present severity 1.

* On a scale of 1 to 5, in which 5 represents the greatest severity.

11. (A156,404) Female, aged fifty-five years, goiter twenty-four years, thyroidectomy right lobe six years ago for doubtful exophthalmic goiter, remission until recent onset of cardiac distress.

The first 4 cases may be grouped with 5 others previously reported[1] in which only the ganglia removed at operation were examined. In these 9 cases of acute progressive hyperplastic toxic goiter, there was very marked hyperpigmentation with extentive granular degeneration, and in some cases atrophy of the ganglion cells.

Cases 5 and 6 may be grouped with three operative cases previously reported.[1] These 5 cases showed considerable hyperpigmentation and granular degeneration, though a smaller number of cells were involved than in the ganglia from the cases of the first group.

Cases 7, 8, 9, 10, and 11 may be grouped with 6 other previously reported[1] operative cases. These 11 cases all showed a very marked regression or complete absence of toxic symptoms at the time of operation or death. In the ganglia from all of these the hyperpigmentation and granular degeneration affected a relatively small percentage of the cells present. In many of the cases, however, a marked diminution in the total number of cells present in the ganglion was shown by sections in series including the entire ganglion.

Discussion.

Thus it will be seen that roughly the degree of hyperpigmentation, the amount of granular degeneration, the atrophy and the reduction in the number of cells was in direct relation to the continuation and subsequent remission of the symptoms of hyperthyroidism. Parallel with this, the perivascular connective-tissue and the connective-tissue stroma generally throughout the gland was increased in direct ratio to the time during which the symptoms of hyperthyroidism had continued. In two of the cases there was marked sclerosis of the ganglionic connective tissue.

Though the present number of cases is too small from which to draw positive conclusions, the observations so far seem to indicate that early in acute hyperplastic toxic goiter there is present in the superior cervical, and probably also in some degree in the other sympathetic ganglia, a process which is causing active stimulation, overfunction, and progressive stages of degeneration in the ganglionic cells. As the symptoms of exophthalmic goiter regress, evidence is found in the ganglia of the cessation of this degenerative process in the ganglionic cells not previously changed past recovery. After the acute toxic symptoms have entirely ceased for years, there remains little evidence of the destroyed ganglionic cells, most of the fatty pigmentary remains of the cells apparently having been absorbed.

The problems of the pathologic changes in the sympathetic

ganglia in man have been obscured in the past by the occasional presence of pigment in the ganglion cells from patients who had exhibited no symptoms of involvement of the sympathetic system. Normally, the cells of the sympathetic ganglia in man are relatively free from pigment until adult life. They then may acquire more or less extensive deposits of brown pigment granules, arranged crescentically about the nuclei. The ganglion cells of patients dying of prolonged wasting diseases, such as tuberculosis and cancer, are apt to show an increased amount of pigmentation and in some instances varying stages of degeneration, hyperchromatization, chromatolysis, and granular degeneration. As control material in these respects many ganglia have been studied by methods parallel to those used on the ganglia from the goiter cases.

Controls.

The control autopsy material is as follows:

1. (A139,228) Eight months' fetus. Placenta previa; atelectasis. Ganglionic cells normal; no pigmentation.

2. (A138,548) Eight months' infant. Pneumonia, following operation for hare lip. Ganglionic cells normal; no pigmentation.

3. (A149,999) Female, aged seventeen years. Pituitary tumor. Death following puncture of corpus callosum. Dilatation of heart; acute nephritis; fatty liver. The lymph spaces around the ganglionic cells are much dilated; the cells are shrunken and hyperchromatic, but not pigmented nor degenerated.

4. (A139,228) Female, aged thirty-six years. Placenta previa; mother of fetus Case 1. Normal; no pigmentation nor degeneration of the cells of the cervical ganglia.

5. (P. B. H. No. 61) Male, aged thirty-four years. Acromegaly; colloid goiter. No pigmentation and no degeneration in ganglia found.

6. (A149,288) Male, aged thirty-five years. Congenital cystic kidneys; hematuria. Some pigmentation, but no degeneration of the ganglionic cells.

7. (38 P. B. H. 3289) Male, aged thirty-eight years. Acromegaly. Some hyperchromatolysis and hyperpigmentation; no granular degeneration of cells found.

8. (A136,199) Male, aged fifty-two years. Carcinoma of anterior wall of stomach; acute parenchymatous nephritis. Autopsy five hours after death. Considerable pigmentation of ganglion cells; no degeneration.

9. (A134,342) Male, aged sixty-four years. Carcinoma of stomach; coronary sclerosis; myocarditis; chronic nephritis. Pericellular lymph spaces of ganglia dilated; cells shrunken; feeble staining; little pigmentation; no degeneration.

The operative control material consists of gasserian ganglia

removed from six patients with trifacial neuralgia in the Mayo Clinic, and from one patient in the Peter Bent Brigham Hospital, and one cervical sympathetic ganglion removed in the Mayo Clinic because of its apparent involvement in a male patient fifty years of age in whom the primary lesion had been a persistent branchial cyst. Although the gasserian ganglia in the 6 cases of trifacial neuralgia and the cervical sympathetic in the branchial cyst case, were all the subject of ganglionic or periganglionic chronic inflammatory changes, and although the patients were from forty-one to seventy-one years of age, in none of the ganglia was there found evidence of such extensive degeneration of the ganglion cells as in the cases of exophthalmic goiter. In all the cases, there was more or less increase of pigment over that found in the ganglia of young adults, but in no case was the amount comparable with that found in exophthalmic goiter cases. Destruction of the ganglionic cells was apparently absent.

Thus it is suggested that neither advanced age, chronic wasting disease, nor chronic inflammatory processes necessarily cause degenerative changes in the sympathetic ganglia resembling those in exophthalmic goiter.

Involvement of Other Ganglia.

The question is suggested whether the involvement of the superior and middle cervical sympathetic ganglia in exophthalmic goiter is but a part of a general metabolic disturbance evidenced by similar changes in the sympathetic ganglia elsewhere in the body, or whether it is confined to the cervical sympathetic ganglia alone. In only 4 cases in which the cervical sympathetic ganglia were shown to be involved have we been able to study the ganglia from other portions of the body. In none of these was there positive evidence of involvement other than hyperpigmentation. There was little or no granular degeneration present resembling that found in the middle and superior cervical sympathetic ganglia. These observations will, of course, need to be confirmed by a much larger series of cases, but they suggest that the ganglionic changes in exophthalmic goiter may be confined largely to the cervical sympathetics, and that they may not be a secondary result of a general metabolic disturbance.

Experimental Work.

With a view to determining the possible relationship of the lesions in the sympathetic ganglia to exophthalmic goiter, studies have been made of the ganglia in a number of animals (dogs, goats, spermophiles, rabbits, and monkeys), in some of which many of the symptoms of exophthalmic goiter had been produced by the administration of Kendall's[6] alpha-iodin compound, in others

which had been subjected previously to double thyroidectomy, and in others in which the cervical ganglia had been injected with various bacteria. In only one animal, however, were suggestive degenerative changes found in the ganglionic cells. In this animal, a young male goat, a small amount of a virulent broth culture of *Bacillus bronchisepticus* (the bacillus associated with canine distemper, and an organism which frequently affects the central nervous system), was injected into the right superior cervical ganglion. The animal died twenty-four days later, and necropsy was performed within an hour after death. The superior cervical sympathetic ganglion from the left side and the stellates from both sides were all apparently normal. The right superior cervical sympathetic, which had received the injection, showed at the immediate site of the injection a small area in which the ganglionic cells were completely destroyed and replaced by necrotic tissue. Throughout the remainder of the ganglion the cells were highly pigmented and showed various degrees of advanced degeneration. In fact, the lesions were quite parallel with those in the cervical ganglia removed from patients with acute exophthalmic goiter.

These experiments are being repeated, and will be made the subject of a subsequent report.

In conclusion, I wish to thank Professors Wm. T. Councilman, Harvey Cushing, and Walter B. Cannon, of Harvard Medical School, for kindly permitting me to examine their ganglionic material from autopsies, operations, and animal experiments.

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THE ETIOLOGY OF PELLAGRA: A CONSIDERATION OF VITAMIN DEFICIENCY.[1]

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In a previous communication[2] it was suggested that the relation of corn to pellagra was analogous to the relation of rice to beriberi. The object of the present study was to determine the results of feeding chickens and pigeons on the offal of the corn mill (which is known as corn chops) after the development of symptoms produced by feeding deficient corn products. The second portion of the work has to do with the application of the information obtained by animal experimentation in the treatment of pellagra in man. Soon after starting the present work it became apparent that the milling and cooking of wheat products played an equally important part in the production of vitamin deficiency.

It had been shown by John M. Little[3] that deficient wheat flour caused a form of polyneuritis in man which must be counted true beriberi. W. R. Ohler,[4] prompted by a suggestion from Little, did extensive experimentation and produced the same type of polyneuritis by feeding chickens hominy as had been produced by deficient wheat. The result in both instances was the same as the type of polyneuritis produced with polished rice.

In 1914 Casimir Funk,[5] who had introduced into medicine the term vitamin, and who had seen his theory regarding the causation of beriberi and its remedy verified, suggested that there was the same relationship between the milling of corn and pellagra as had been proved between the milling of rice and beriberi. There was no experimental or clinical evidence presented, however, and the suggestion did not receive the attention it deserved, though the advocates of a deficiency cause never lost sight of the possibility of such a solution. Funk pointed out the marked difference in the composition of corn and of the germ of corn. The fat content of the whole grain is 5 per cent., while the germ contains 30 per cent. The loss of fat was thought by him to be a good indicator of the loss of vitamin, as there was evidence to show that the fatty portion contained the vitamin. South African and American corn were both deficient, but the latter more so because of the higher degree of

[1] Presented at the meeting of the Association of American Physicians in Washington, May 10, 1916.

[2] Wood, E. J., Vitamin Solution of the Pellagra Problem, Jour. Am. Med. Assn., May 16, 1916, vol. lxvi.

[3] Jour. Am. Med. Assn., 1912, lviii and 1914, lxiii.

[4] Jour. Med. Research, vol. xxxi (new series, vol. xxvi).

[5] Prophylaxe u. Therapie der Pellagra im Lichte der Vitaminlehre, Munchen. med. Wchnschr., 1914.

milling. Funk was disposed to regard the mortality rate of the disease as an index of the degree of deficiency.

It had been shown in the beriberi work that phosphorus pentoxide was a reliable indicator of vitamin, though there was no direct connection between the two. The same value is attached to it in the present work. Sulphur determination is being introduced by us as an aid in determining vitamin, but the work has not progressed far enough to justify any definite conclusions as to its value in comparison with the phosphorus indicator. So far the results obtained show a striking similarity.

Viewing pellagra as a deficiency disease, and attributing the deficiency to the milling process or to some chemical change which brings about destruction of vitamin in the process of cooking, it is no difficult matter to reconcile and even harmonize many of the views of the early Spanish, Italian, and French pellagrologers. The vast amount of literature which has accumulated since the publication of Casal's[6] original article has been very lifeless until recently. It now becomes reanimated by recent progress, and a careful study of this wealth of material is not only interesting, but of practical value, and we are filled with admiration at the keenness of the observation of those men who had so little opportunity for the accurate study of such a problem, and whose observations have stood so well the test of modern scientific advance. Sandwith[7] states that as early as 1707 Pedro Casal wrote in Spanish that pellagra was due to insufficiency of diet. In the latter part of the eighteenth century Franzago declared that maize was unhealthy only because it was an insufficient food, but he would not say it was the sole cause. Later, Marzari[8] claimed that the cause of the noxiousness of the corn was an insufficiency of gluten. Had there been a knowledge of Funk's theory of vitamin during that period in which corn was connected with pellagra in one way or another, the problem would probably have been solved long ago. The school of Lobroso had as a basis of its teachings a definite toxicity which may now be interpreted in terms of deficiency.

The germ of the corn lying at the hilus of the grain is poorly protected and subjected to the action of all injurious agencies both animal and vegetable. Damaged corn is always most affected in this part. Owing to the high fat content, the method of removing the germ before the grain was finally ground was introduced. This process was called "degermination." It is practised in many places and in many types of mill.[9] The two products of this form of milling are granulated corn meal and corn chops. The latter is spoken of

[6] Historia natural y medica de el Principado de Asturias. Abra posthuma del Doctor D. G. Casal, Medico de Su Magestad y su Protomedicin de Castilla, Madrid, 1762.

[7] Trans. Soc. Trop. Med. and Hyg., October, 1915.

[8] Essai Medico-politique, 1810.

[9] Farmer's Bulletin, 298, U. S. Dept. Agr.

as the offal of the corn mill and is sold as cattle food. In former times the grain was ground whole at the community water mill and there was no damage from the great heat which may be produced in rapid steam milling. This form of heat, however, is inconspicuous in comparison with the heating process which the grain often undergoes before reaching the mill.

The differences between corn chops and corn meal are given below:

	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Fiber, per cent.
Meal	9.2	1.9	74.4	1.0
Chops	9.0	7.0	70.0	9.0
Germ alone	21.7	29.6	44.7	
Endosperm	12.2	1.5	85.0	

Analysis of the various articles of food which were experimented with showed interesting variations in the P_2O_5 content. It was readily apparent that the cortex of the various grains, as has been formerly held, contained the bulk of phosphoric acid. It was also apparent that the amount was influenced by the degree of fineness of the product. Wheat middlings sifted in the laboratory with the removal of only the very smallest amount of bran showed a definite decrease in the phosphorus.

	P_2O_5, per cent.
Corn chops	1.15
Water-ground meal (North Carolina)	0.78
Whole meal, steam milled (Virginia)	0.60
Highly milled meal (Ohio)	0.29
Steam-milled meal (North Carolina)	0.58
Wheat middlings (offal of mill)	0.98
Whole-wheat flour	0.50
Average wheat flour (bought in Wilmington, North Carolina)	0.14

The first important suggestion of a vitamin deficiency caused by the milling process was made by P. A. Nightingale[10] in Rhodesia in 1912. He found that prisoners fed on highly milled meal developed a definite group of symptoms for which he coined the word "zeism," thinking it to be a new condition. There can be no doubt that this condition was acute pellagra, which has never been reported in medical literature except in the Southern States, in which it appeared in 1905. All references in European literature recognize pellagra only as a chronic process. Nightingale concluded that the use of highly milled meal had caused the disease, and substituted whole meal which was ground by hand in the jail. The result in his words was "immediate and magical."

Recent studies in polyneuritis gallinarum in its relation to beriberi now become of great value in suggesting a line of investigation in pellagra. Goldberger[11] has emphasized the importance of viewing

[10] Nightingale, P. A., Transvaal Med. Jour., 1912.

[11] Public Health Reports, June 24, September 11, October 23, 1914, Jour. Am. Med. Assn., October 10, 1914, and February 12, 1916, Public Health Reports, January 15, 1915.

pellagra in much the same light as beriberi, and we are indebted to him for the suggestion. It is not known that there is any connection between pellagra and beriberi, except that both diseases are probably deficiencies. Any experimental work in pellagra would, therefore, not be aided by a study of polyneuritis in fowl. The present work was undertaken to prove the fact that polyneuritis could be caused by meal made deficient in the milling process and cured by the portion of the grain removed in the production of the deficiency. Unexpected findings have thrown considerable light on the question, and have tended to suggest the possibility of a disease condition which seems to be due to a deficiency not so marked as to be sufficient to cause polyneuritis. It would seem that beriberi and pellagra, then, differ only in the degree of insufficiency.

The recent work of Voegtlin, Myers, and Sullivan[12] showed that vitamin was promptly destroyed by the use of soda and certain baking powders in the preparation of bread regardless of the original quality of the flour or meal. It was further shown that this could be prevented by the use of sour milk in conjunction with the alkali. Some baking powders contain enough tartaric acid to neutralize the sodium carbonate after the liberation of carbon dioxide. It is an interesting study to trace the introduction of this form of cooking and the appearance of pellagra, just as it is interesting to study the time connection between the introduction of highly milled meal and the disappearance of the old water mill which ground the corn *in toto*. In one community, at least, I have been able to show that the year which marked the abandonment of the old mill was the year of the appearance of the first cases of pellagra. Pellagra was unknown in the Confederate army, though lack of food was frequent; but there was no deprivation of the grains of any portion in the milling. There are broad areas in North Carolina in which pellagra has never occurred, though poverty and poor hygiene obtain in the fullest. These areas are separated from railroad travel, and home products are used through necessity. This is particularly true of the remote mountain counties. I have searched diligently through four such counties and have never been able to find the disease, nor could I learn of its occurrence from the physicians. But as the Piedmont section is reached and the people are able to procure manufactured products of every sort, the disease soon appears and reaches its high-point in the cotton-mill village, in which highly milled products are used almost exclusively and soda is added to every form of food to hasten the cooking (Voegtlin, Myers, and Sillivan).

Six pigeons were placed in a roomy cage outdoors with a floor to prevent the scratching of the earth. The best pigeon grit was abundantly supplied as well as plenty of fresh water. Whole corn was

[12] Public Health Reports, April 14, 1916.

broken in the laboratory and allowed in great abundance. No other food was given throughout the experiment. For four months there were no developments of disease, though it was evident that conditions were not best suited for growth and development. At one time it was noted that there was some droopiness, and investigation showed that the corn used at the time was of an inferior quality. From that time seed corn was used. This group were the controls.

In the second group of pigeons the food was corn meal with a P_2O_5 content of 0.58 per cent. After ten days it was noted that the pigeons had red legs in striking contrast to the controls, though of the same breed and age. In addition to the red legs there was marked droopiness and inactivity. After six weeks a more deficient meal with a P_2O_5 content of 0.29 per cent. was substituted. There was no change except increased redness of the legs. After these twelve weeks there had occurred only one death, and that from a cause having no bearing on the experiment. At this time it was decided to produce polyneuritis gallinarum if possible. Wellman and Bass[13] as well as Ohler had produced polyneuritis in less than three weeks on a diet better than the one in use by us. The most deficient meal was made into bread, with the addition of soda. After a month of this feeding there was still no polyneuritis. During the experiment two squabs had been hatched from eggs laid after the experiment had been several weeks under way. These squabs did very well until the time for them to feed themselves. In a very few days polyneuritis developed. By the administration of corn chops there was prompt relief. It is a notable fact that these young pigeons were the only victims of polyneuritis, though the diet was such that it was to be expected that none of the animals would escape. The successful feeding of corn chops proved for corn what had already been proved for rice and wheat. By alcoholic extraction a substance was found in the corn chops which was equally as effective as the alcoholic extract of rice polishings had been in former experiments.

It appeared that continued feeding of a gradually increasing deficiency diet resulted in the acquiring of a peculiar kind of tolerance which may later be shown to explain some of the peculiarities of pellagra. After red-legged pigeons had been kept on the same food for several weeks it was impossible to produce polyneuritis with the most deficient diet, and the red-legged condition was just as promptly relieved by feeding corn chops as was polyneuritis. Only a few days were required for a return to normal, though it was found that the longer the red-legged condition had existed the longer the time required for a complete subsidence.

Chickens hatched on the same day were divided into two groups.

[13] Am. Jour. Trop. Dis. and Prev. Med., 1913.

One group was fed deficient corn meal while the control group was fed corn chops. The food of the deficiency group contained 0.58 per cent. P_2O_5 in the beginning, which was later replaced by a meal with a 0.29 percentage. The red-legged condition did not occur, but the chickens did poorly. There was one case of polyneuritis gallinarum which did not respond to treatment because discovered late. The growth in every case was below normal and droopiness was quite marked. At the end of the experiment the chickens fed on corn chops had gained 8 per cent. more than those on deficient food.

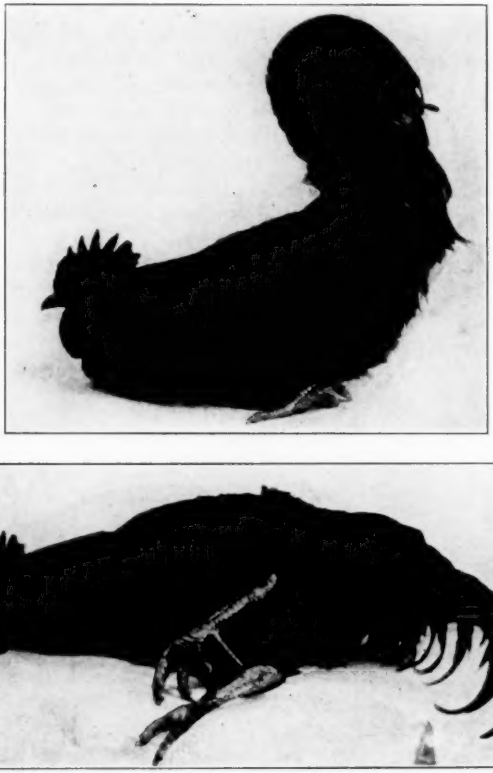

FIG. 1.—Photographs of a Rhode Island cock, showing complete paralysis: a definite case of polyneuritis gallinarum caused by feeding cooked hominy.

Through the courtesy of a colleague we were given the opportunity to study polyneuritis gallinarum in a Rhode Island Red cock. The cause was cooked hominy. The photographs show the extreme degree of paralysis and the prompt recovery after the

administration of the extract of corn chops and a diet of the same food. This animal became neuritic by a change of diet which was not extreme, and at no time was there any confinement as in the experiments above recorded. The range was ample and the animal had abundant opportunity to supplement the hominy with other food. This suggests other factors not yet understood which play a part in deficiency conditions.

FIG. 2.—Photograph of the same cock forty-eight hours after feeding corn chops and the extract of corn chops. Improvement was immediate. Recovery was complete.

The red-legged condition was very definite and the cause was well established. The cure was equally simple. It would be beyond the scope of this work to attempt to show that the condition was analogous to pellagra as polyneuritis gallinarum is to beriberi. Suffice it to say that the observation was of the greatest help to us in our work, and by it we were able to determine very exactly the quality of the grain, for it was a very delicate indicator. We were disposed to regard polyneuritis as the result of a total deficiency and the red-legged condition as a partial deficiency. If this can be applied to pellagra it is readily understood why the coolie of the East has beriberi while in the South the deficiency disease is pellagra. The coolie eats one food and there is no chance for making up the deficiency with other foods. In the South there is always more than one food, and therefore the deficiency is made up in part at least.

Why it was impossible to produce polyneuritis gallinarum in the pigeons with the red-legged condition we cannot say. In several pellagrins we found polyneuritis which much resembled beriberi, though such a diagnosis was not ventured because of the frequency of the use of excessive dosage of arsenic in the disease. It is very probable that many cases of neuritis in pellagra have been caused in this way.

Feeling justified in the opinion that the portion of the grain removed in milling contained the vitamin, the lack of which caused pellagra, it was decided to feed pellagrins on exclusive diet of corn chops.

CASE I.—A white man, aged sixty-five years. Symmetrical erythema of the backs of the hands, stomatitis, diarrhea, prostration, and emaciation. For several months the diarrhea had been troublesome, and the number of stools varied from six to ten in twenty-four hours. On Wednesday morning he was placed on an exclusive diet of corn chops, but allowed a little butter. The corn chops was baked as bread without soda or baking powder, and was also made into a gruel. The patient was fed five times during the day. It was explained to him that the remedy was in the food and could not be successfully extracted. After forty-eight hours the relief was most striking: the diarrhea had ceased, the stomatitis was relieved, and desquamation was progressing rapidly. On Sunday he was discharged, with only the one complaint, constipation, to be considered. He was kept under observation for several weeks in the dispensary, and there occurred no recurrence.

CASE II.—A white man, aged fifty-six years. The backs of his hands were covered with a bullous erythema and the redness was intense. The first physician who saw him suspected a dangerous skin infection. The lesions were perfectly symmetrical. There was a complaint of stomatitis and diarrhea. In addition the patient was a diabetic. He was placed on a diet of corn chops, and at the end of four days the skin lesions were relieved and exfoliation was progressing rapidly, the diarrhea and all other symptoms had ceased. After a few days he was given the Allen fast and treated for the diabetes, with prompt disappearance of sugar. After three months there has occurred no recurrence of pellagra.

CASE III.—A well-conditioned white woman, aged twenty-two years. She had many peculiarities of diet, and as a result was suffering from pellagra of a typical type. The erythema covered the backs of her forearms, and there was a classic Casal collar. She complained of diarrhea and stomatitis. After four days of corn chops she was relieved of all symptoms, and at the end of a week desquamation was complete. After two weeks of this treatment she had gained eight pounds and felt better than in years. She was allowed other things besides the chops, but was required to eat the latter at least three times a day.

It was found that far-advanced cases were not relieved in this striking manner, though improvement often followed, and the treatment was well justified. After a time structural change takes place both in the intestinal tract and the nervous system, and no treatment can avail anything. This is equally true of other diseases for which there are specifics.

CASE IV.—A negro woman, aged about thirty years, was admitted to the hospital in a hopeless condition. She was far advanced in dementia. The bowels and bladder were being emptied in the bed, and the patient required an attendant constantly to keep her in bed. It was impossible to feed her except by the tube, which was used three times in the twenty-four hours. At each feeding a pint of milk and three eggs were given. There was some improvement, but it was not marked until four ounces of a gruel of wheat middlings was added. The intestinal condition improved promptly, and there would be periods of entire freedom from the diarrhea. The mental condition also improved, and the use of the tube was abandoned. The patient died rather suddenly from an unknown cause. In spite of the unfavorable termination there could be no doubt that the food caused improvement, and more markedly when the food containing grain cortex was added.

In all cases treated by the feeding method no drugs were used except an occasional placebo. It was soon learned that the corn chops to be effective must be freely milled. Just how this can be worked out practically remains to be demonstrated by some reliable dealer. Whatever the essential substance is there can be no doubt that it is very unstable, and apart from this, owing to the occurrence of rancidity, corn chops keeps very poorly. Some chemical process may be introduced to extract from the corn chops or the wheat middlings the essential substance. Our own efforts along this line, while proving that such a substance was present and could be extracted, were too expensive for practical purposes because of the great amount of alcohol necessary. Mr. G. F. Catlett was able to secure 65 c.c. of a watery substance from one kilo of corn chops by extracting with 8000 c.c. of 95 per cent. grain alcohol. The same general plan was followed as had been formerly used in the preparation of rice polish extract. The product made in our laboratory from corn chops was certainly as effective as rice polish in polyneuritis gallinarum when that condition was caused by defective corn. There is no reason to believe that it would not have been equally as effective if the polyneuritis had been caused by polished rice. Certainly in pellagra we were able to relieve the symptoms by the use of wheat middlings in one case and corn chops in others. This suggests that there probably is no specificity in the vitamin, but that all grains under discussion yield a certain amount, and that the only difference is one of richness.

While the bulk of our experimental work was confined to a con-

sideration of corn deficiency, we are entirely in accord with those observers who regard the wheat as a more frequent source of the deficiency in the South at this time. We were in a position to study the corn question, and were desirous of explaining in the beginning why polenta, the national dish of the Italian peasantry, caused pellagra. It can be readily accepted now that the toxicity of Lombroso was really a deficiency, and that the food forming almost the exclusive diet of the people under his observation was polenta. Polenta is a thick corn-meal mush, which was kept for days after its cooking, and which usually underwent fermentation. It has been shown that when corn is deficient the germ is usually the portion of the grain first and most seriously damaged regardless of the source of injury. Much of this Italian corn was badly damaged, and therefore was deficient because the vitamin had been destroyed in the germ. We will later study the result of fermentation on the vitamin content of polenta.

It is obvious that vitamin deficiency of the grain food may be replaced by an abundant protein diet of fresh lean meat, fresh milk, eggs, and various other expensive foods. It is also obvious that an infant may be protected from scurvy while on a faulty diet by giving such an antiscorbutic as orange juice. But is there justification for such a procedure? With the gradually increasing cost of foods of the vitamin supplying type, the poor whites of the South are no nearer their salvation from this great scourge. Lombroso once said that it would be equally as effective to advise his patient to be rich as to advise the diet needed, and if the patient were rich he would not have to be advised about the diet, for his natural desires would protect him from the disease. If decortication of grain and faulty methods of cooking cause the disease, the remedy is not beyond the reach of the poorest pellagrin. And this is our experience. It is, of course, granted that the high protein diet is most desirable, but the practical solution of the pellagra problem in the South calls for some other remedy. It can be easily shown that people live without meat, milk, eggs, and other expensive protein, and still do not suffer from pellagra. Our experience is that such people do not eat decorticated grains. We have also learned, as pointed out on a previous page, that the response from feeding pellagrins the decorticated portions of the grain is more prompt than when the diet is meat and eggs. It is to be hoped that the vitamin preparation of A. Seidel,[14] which is prepared from brewer's yeast, using Lloyd's reagent, will be an inexpensive source of making up the deficit in the diet of the pellagra class. We have had no opportunity to test it in the treatment of the disease.

It would appear to us that pellagra is readily prevented; that the prevention does not require any increased cost of living; that the

[14] Public Health Reports, 1916.

use of whole grains that have not undergone destructive changes and the avoidance of alkaline rising agents would entirely eradicate the disease.

It gives me pleasure to acknowledge my debt to Mr. G. F. Catlett, who by his sympathetic advice and aid in the chemical portion of this study has made it possible.

SALVARSAN IN THE TREATMENT OF DOUBLE INFECTIONS, TUBERCULOSIS, AND SYPHILIS.[1]

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The universal employment of the Wassermann reaction has revealed the striking frequency of an unknown or an unacknowledged syphilitic infection in patients with tuberculosis. The greater participation of careful internists in the problems of lues and the development of more recently devised tests have been responsible for showing that either as a result of their disease, or of its vigorous treatment, syphilitics exhibit an increased susceptibility to tuberculosis. Recent experience with the late lamented Paul Ehrlich's epoch-making drug, salvarsan, promises hope for the future in the treatment of patients afflicted with these combined infections, and very likely the diminution of syphilitics' susceptibility to the great white plague.

In ten years of prison service, Tedeschi[2] found that 70 per cent. of the cases of pulmonary tuberculosis had developed upon a luetic soil.

Among 346 tuberculous inmates of Boucicaut Hospital, 19 per cent. (64) gave a positive Wassermann reaction, although but 3 per cent. (10) acknowledged a previous luetic infection or showed any signs of it.[3] Among 116 patients at Brompton Hospital with pulmonary tuberculosis selected at random by Inman,[4] he found only 5 per cent. (6) positive. The admissions to a children's orthopedic hospital in Sweden[5] during three years included 29 affections

[1] Read by title before the clinical section at the Eleventh Annual Meeting of the National Association for the Study and Prevention of Tuberculosis, held at Seattle June 14 to 16, 1915, but not completed in time for publication in the Transactions.

[2] Studium, Napoli, 1910, iii, 343, 377.

[3] Bull. Acad. de méd., Paris, 1914, Series 3, lxxi, 596. (Abst.) Jour. Am. Med. Assn., Chicago, 1914, lxii, 1848.

[4] Compt. rend. Soc. de biol., Paris, 1914, lxxvi, 254.

[5] Norsk. Mag. f. Laegevidensk, Christiania, 1915, lxxvi, 557–696. (Abst.) Jour. Am. Med. Assn., 1915, lxiv, 2030.

of the knee, of which 20.7 per cent. were non-tuberculous while two-thirds of this percentage were plainly luetic, with a positive Wassermann reaction. This test was also positive in many other cases at the hospital, and in a large number with unmistakable tuberculous lesions, and for the most part in children with latent syphilis (in reality inherited lues), although called "scrofula." Among 22 more recent admissions to the same hospital, all of whom were recommended with the diagnosis of some form of tuberculosis, 23 per cent. (5) showed a positive Wassermann reaction.

Among 47 patients with lues at various stages of the disease tested with tuberculin by the intradermic method of Mantoux, 94 per cent. (44) showed a strongly positive, 4 per cent. (2) a doubtful, and 2 per cent. (1) a negative response; while in 28 of these cases a von Pirquet test showed 75 per cent. (21) positive, 14 per cent. (4) doubtful, and 11 per cent. (3) negative reactions.[6] In comparing these figures with the ones Mantoux himself obtained in 91 cases of known tuberculosis (81 positive reactions, or 89 per cent.; 3 negative, or 3 per cent.) the observers concluded there was too slight a difference to be of striking diagnostic value; but called attention to the more intense and persistent intradermic reaction to tuberculin in the syphilitic patients than in those in whom tuberculosis alone existed.

Bronfenbrenner's[7] recent experience with the complement-deviation test, employing Besredka's tuberculin, indicates that the incidence of tuberculosis is very much higher among syphilitics than among non-syphilitics, and probably because lues itself or antiluetic treatment markedly lowers the resistance, and so renders such individuals either more susceptible to the acquisition of or less resistant against the awakening or progress of a previously contracted tuberculosis.

Numerous articles and reports of cases more and more accurately studied from the clinical, therapeutic, bacteriological, pathological, and recently from the radiographic and serological point of view have clarified our conception of uncomplicated pulmonary lues, and lessened the difficulties in respect to both the diagnosis and the treatment of co-existing luetic and tuberculous pulmonary infections.[8] Stengel[9] carefully analyzed the more authoritative literature upon pulmonary syphilis, and suggested that the discrepancy in the published statements of the frequency of acquired, as contrasted with hereditary lues of the lung, depended upon whether

[6] Nicolas, Favre, and Charlet, Lyon méd., 1910, cxiv, 624.

[7] Arch. Int. Med., Chicago, 1914, xiv, 786.

[8] Am. Jour. Med. Sc., Philadelphia, 1905, cxxix, 563. New York Med. Jour., 1913, xcviii, 600. Councilman's papers quoted Johns Hopkins Hosp. Bull., Baltimore, 1891, ii, 34. Med. Contemp., Lisb., 1912, xxx (Abst.), Jour. Am. Med. Assn., 1912, lix, 1932. Hosp. Tid., Copenhagen, 1914, lvii, 321–352. (Abst.) Jour. Am. Med. Assn., 1914, lxii, 1370. Rev. gén de clin. et de thérap., Paris, 1914, xxviii, 86.

[9] Univ. Penn. Med. Bull., Philadelphia, 1903–1904, xvi, 89.

the author was a clinician or a pathologist; the former, accepting the accuracy of such a diagnosis upon insufficient evidence, and the latter, aided only by the old histological methods, excluding many a suggestive case if studied in accord with modern technic.

A wave of therapeutic enthusiasm for mercury and even for the iodides engulfed many clinicians and institutions devoted to the care of tuberculous patients in the nineties, and, as was natural, some good but much harm was done.[10] With evidence of a previously acquired, or an inherited syphilitic infection a beneficial effect from one or both these remedies is readily understood and should be expected;[11] but there is no convincing proof that any benefit will result from the use of mercury or iodide of potash in the tuberculous who are not at the same time luetic. There is, on the contrary, much evidence of danger attending the vigorous use of these drugs, especially of mercury[12] in tuberculous patients with a tendency to hemoptysis, and of the iodides, as a result of their congestive effect.

Although Ehrlich[13] originally included advanced cases of tuberculosis among the contra-indications to the use of salvarsan, subsequent clinical reports show that with care such individuals need not be deprived of the assistance afforded by the new remedy.

Herxheimer and Schonnefeld[14] first reported the use of salvarsan in a luetic patient with pulmonary tuberculosis. After a four weeks' course of intensive mixed treatment had failed to modify the testicular lesion of a patient plainly infected with both diseases, salvarsan (0.5) was given. The resulting benefit was immediate and striking, but no details of its effect, if any, upon his double apical pulmonary lesion were cited. Treupel[15] described an advanced case of pulmonary tuberculosis in a physician, aged thirty-three years, in whom the faithful and vigorous use of mercury inunctions had not cured a luetic infection of a year's duration. Intramuscular injection of salvarsan (0.6) produced quite a severe reaction at the bilateral sites of inoculation; and at first considerably upset the patient, with a maximum temperature of 38.5° on the second day. The writer noted the beneficial effect upon the symptoms referable to syphilis, and stated that the pulmonary condition was unchanged. Gluck[16] cites a serious case of malignant syphilis with fever and with a pulmonary catarrh very favorably influenced by one injection of salvarsan (0.4), but gives no details about the lung condition before or after treatment.

[10] Wien. Klin., 1895, xxi, 259.
[11] New York Med. Jour., 1908, xxxviii, 385.
[12] Jour. Am. Med. Assn., Chicago, 1910, lv, 915.
[13] Abhandlungen über Salvarsan, J. F. Lehmann, München, 1911, i, p. 391; 1912, ii, p. 554.
[14] Med. Klin., 1910, vi, 1400.
[15] Deutsch. med. Wchnschr., 1910, xxxvi, 1393.
[16] München. med. Wchnschr., 1910, lvii, 1638.

In an analysis of 375 cases treated with salvarsan, Sieskind[17] states that he has treated patients with hemoptysis and with phthisis in varied stages without ill effect, and always with general improvement and an increase in weight. Among the indications for its use he includes luetic patients with tuberculosis, in whom mercury affects the tuberculosis adversely. Treupel and Levi[18] state that they have injected salvarsan into syphilitic patients with open pulmonary tuberculosis without unfavorable effects on the latter disease, except possibly in two cases: one a patient with an old apical tuberculous process in whom an intramuscular injection was followed three weeks later by temperature and an exudative pleurisy; and another who developed a croupous pneumonia upon the same side as and two weeks after an interscapular injection, which had been followed by an extensive and persisting deep infiltration. Herxheimer and Altmann[19] administered salvarsan to 9 patients with glandular, cutaneous and pulmonary tuberculosis (and also experimentally to animals), and called special attention to the resulting focal reaction, apparently identical with that produced by injections of tuberculin. Although they selected only small doses no beneficial effect upon the tuberculous process was detected. In 4 cases of lupus this focal reaction was especially well studied: it consisted of pain, heat, swelling, and redness, appeared within four to six hours after the injection, lasted about twenty-four hours, disappeared with scaling, and its intensity apparently ran parallel to the degree of the disease. Reinjection produced a less vivid effect. No benefit was noted in the skin lesion in 3 of the cases after three injections following each other within three or four weeks. They compared it to the so-called Herxheimer's reaction and liken it to a mobilization of tuberculin. In a patient with secondary lues and tuberculous cervical glands the administration of salvarsan (0.5) was followed by a focal reaction with subsequent softening and pus formation (bacilli positive), necessitating a later operation. In two of their patients with pulmonary tuberculosis the second dose of salvarsan was followed by a general as well as a focal reaction (cough and rales). A fourth patient with a healed apical process developed a local, focal, and general reaction five days after the injection of salvarsan (0.5) into the gluteal region, and showed at autopsy an induration and encapsulated caseation in the lungs; but the cause of the sudden death was a pulmonary embolus from a thrombus in the femoral vein, secondary to a streptococcus abscess at the site of inoculation, and had nothing to do with the coexistence of tuberculosis. Bine[20]

[17] München med. Wchnschr., 1910, lvii, 2027.

[18] Ibid., 1911, lviii, 237, 305.

[19] Deutsch. med. Wchnschr., 1911, xxxvii, 441. Arch. f. Dermat. u. Syph., Wien u. Leipzig, 1911, cx, 249.

[20] California State Med. Jour., Sacramento, 1911, ix, 255.

gave salvarsan to a patient with glandular tuberculosis and a positive Wassermann, but his report does not mention the results. Fordyce so treated Harris's[21] patient with pulmonary tuberculosis and tertiary lues (extensive nasal necrosis) with an excellent effect upon the latter disease; but neither details of the physical examination of the chest nor the effect of the medication upon the former disease are available, and the patient cannot be traced. Despite the coexistence of an apical catarrh, 2 of Schiele's[22] patients with tertiary lues derived benefit from the intramuscular injection of salvarsan (to one 0.3 twice to the other 0.5). Although the condition of his third patient scarcely justified resorting to salvarsan (0.3 lumbar) and was followed by a rather severe reaction, her subsequent marked improvement and the elapse of two and a half months before she died, render decision rather difficult as to the responsibility of the drug. The dose, however, was larger than would be selected today. This patient was aged twenty-nine years, under-developed, poorly nourished, deaf, with hereditary lues of a progressive type, with double apical consolidation, bronchial breathing at one apex and severe cough, with a large hard liver, an enlarged spleen, a tender, painful, resistant abdomen, copious diarrhea, a perforation of the hard palate, a negative Wassermann, and with a still unhealed sinus from an operation upon one mastoid nine months previously. She died after a recurrence of diarrhea and severe abdominal pain. Jacquet[23] administered salvarsan, 0.6 (intragluteal), to a male, aged forty-two years with pulmonary tuberculosis of the second stage, left pleurisy, luetic lesions of foot soles, testicle and epididymis, and a positive Wassermann. Although not known at the time of inoculation the patient had had an hemoptysis a short time before. The effect of the treatment was strikingly good upon the luetic process, the general condition, and even upon the active pulmonary signs. In addition to the 2 fatal cases cited above (Herxheimer and Altmann, Schiele) Wechelmann's[24] collection of deaths following the use of salvarsan includes 10 others, exhibiting clinical or postmortem evidence of the existence of both tuberculosis and lues. The existence of the former evidently had nothing to do with the effect of the drug or with the fatal termination in 5 of them. If his meager details can be relied upon for judgment, neither of Dind's 2 cases were in a condition to justify the use of salvarsan, although the one with pulmonary and meningeal tuberculosis, admitted in coma and injected only as a last resort, was given but 0.1. Schlæsberg's case with tertiary lues had phthisis and also chronic

[21] Laryngoscope, St. Louis, 1911, xxi, 201, 671.
[22] St. Petersb. med. Wchnschr., 1911, xxxvi, 359.
[23] Bull. et mém. Soc. méd. d. hôp. de Paris, 1911, Series 3, xxxii, 567.
[24] Ueber die Pathogenese der Salvarsantodesfalle, 1913, Urban and Schwarzenberg, Berlin, Wien.

nephritis, and was given salvarsan (0.4) about twelve weeks after a course of seven injections of mercury, which had not been well tolerated. Autopsy, however, pointed to nephritis as the cause of death. Vorner's[25] fatal case, with the history of lues dating back twenty, and of tabes ten years, was given salvarsan (0.6), followed within twenty-four hours by a chill, fever, rapid pulse, headache, nausea, and vomiting; the urine contained 1 per cent. albumin, the temperature persisted for six days, and the patient continued to be nauseated and very weak for about seven days; at the middle of the second week, insomnia and further exhaustion; at the fourth week, condition more serious, afternoon fever, nausea, a painful tender rigid abdomen, diarrhea, enlarged liver, increasing exhaustion, and death. Autopsy disclosed a general miliary peritoneal tuberculosis and enlarged softened mediastinal glands, histologically tuberculous. The author attributes the result to a hyperemia of the glands and a proliferation of the tubercle bacilli; likens it to a Herxheimer reaction, and claims that salvarsan is liable to activate any latent infection, including tuberculosis. Despite his statement that the physical examination revealed nothing noticeable about the internal organs, no such advanced and extensive tuberculous lesions as were disclosed at autopsy could have developed within five weeks of the injection of salvarsan; and his selection of so large a dose for a patient in such a wretched condition was, in view of our present experience, injudicious. The internal organs were also recorded as normal in the physical examinations of two of Finger's fatal cases; in both of which a chronic glandular tuberculosis was disclosed at autopsy to be the source of the active fresh lesions at the base of the brain and elsewhere. To one of them a second dose (0.4) was administered, despite a warning reaction after the first injection and the persistence of headache; and to the other, even a third dose (0.4), although after a long interval; but despite the warning of a Herxheimer reaction which followed the first dose; and the patient's complaint, at the time of the final injection, of severe pains in ears, headache, and malaise. These three fatalities suggest more care in preliminary examination and the selection of smaller doses. Wechselmann urges a carefully studied spinal puncture before administering salvarsan to tuberculous patients complaining of headache. Audry[26] gave arsenobenzol (0.3) to an anemic woman, aged twenty-six years, who had a tuberculous involvement of one apex, and who, six years previously, had shown symptoms of and had received some treatment against an unacknowledged luetic infection. Decided improvement in both diseases followed, but a second dose (0.3), administered seven months later on account of a recur-

[25] Monatsh. f. prakt. Dermat. Hamberg u. Leipzig, 1911, liii, 591.
[26] Ann. de Dermat. et Syph., Paris, 1913, 5 s., iv, 98.

rence of specific cutaneous symptoms, was followed by vomiting, an increase in the cough and considerable bloody sputum. The latter disappeared after three days, but no alteration in the pulmonary signs could be detected. McDuffie[27] gave salvarsan to hopeless cases of tuberculosis, but his report lacks all details. Robinson[28] found that an injection of salvarsan (0.4) to a patient with pulmonary tuberculosis and lues was followed by a rapid decrease in the amount of sputum; and that (0.6) produced no ill effect upon the tuberculous lesion in another patient who exhibited an active process and who became infected with syphilis. In 9 patients with different stages of tuberculosis, Courmont and Durand[29] tested the effect of Billon's arsenobenzol, administered in the form of enemas (eight doses twice a week of 0.1 in 5 c.c. of warm saline, properly alkalinized). Two of these patients were also luetic: one, a tabetic, aged forty-three years, with extensive fibrocaseous tuberculosis, in whom the treatment seemed to aggravate the pulmonary condition and diminish his weight, although his pains were alleviated; the other, but without bacilli in the sputum, with a chronic fibrous consolidation at one apex, and the history of numerous attacks of pleurisy was much benefited. Robin[30] commends the recent abandonment of mercury in favor of salvarsan for patients with co-existing lues and tuberculosis, and especially if a tuberculous patient becomes infected with syphilis and whenever the latter disease takes a grave course. He cites the case of a male, aged thirty-three years, with a tuberculous family history and evident signs of chronic fibroid tuberculosis since the age of twenty. For three years past some signs of activity, quickly relieved by rest. He contracted syphilis eight months ago, was very inadequately treated with mercury benzoate. His pulmonary signs and symptoms rapidly increased and to secure a prompt action he was given three successive doses of salvarsan with excellent results.

With due regard to the usual contra-indications, Klokow[31] tried the effect of salvarsan (0.2 to 0.6) upon twelve tuberculous sanatorium patients with visible luetic manifestations and positive Wassermann reactions. Only one dose of salvarsan (0.4) was given to the first six, classified as in the first stage and without tubercle bacilli, and all did well. They were from twenty-two to thirty-seven years of age. One was a patient with beginning secondaries; another, denying a luetic infection, showed a positive Wassermann; and in the remaining four, syphilis had been contracted from three

[27] New York Med. Jour., 1913, xcvii, 551.
[28] Month. Cycl. and Med. Bull., Philadelphia, 1913, vi, 333.
[29] Lyon méd., 1913, cxxi, 97. Bull. Soc. méd. des hôp. de Lyon, 1913, xii, 466, 536.
[30] Clinique, Paris, 1913, viii, 338. Riv. internaz. di clin. e terap., Napoli, 1914, ix, 69.
[31] Berl. klin. Wchnschr., 1913, l, 1754.

to eleven years previously. Two showed a subsequent but very insignificant general reaction, and one a very slight and transitory rise of temperature. None exhibited any focal reaction. To the second 6, in the second and third stages of pulmonary tuberculosis, he gave one or more doses according to their condition. During the treatment two lost their bacilli and have remained without bacilli since; and the pulmonary lesions of three of them showed improvement. In none of the 12 could he detect any ill effects which could be attributed to the salvarsan treatment. All who were in a sufficiently good social condition to obtain proper care improved generally. A summary of the latter 6 cases follows: Case VII, aged thirty-eight years, pains in chest, apathy, anorexia, for six years frequently unable to do his work, symptoms intensified for eleven months, plus cough, expectoration, fever, profuse night sweats, weakness, loss of weight; right upper, fairly extensive process with rales, right lower, pleural rub and emphysema, left, slight, inactive lesion; Wassermann, von Pirquet, and tubercle bacilli positive, marked red scleræ: when apyretic, salvarsan (0.25), no discomfort, no fever, but a transitory focal reaction in lungs and scleræ; eighteen days later, salvarsan (0.3), in six hours fever, followed by general and focal reaction, then prompt improvement; two months later, both general and local improvement, tubercle bacilli absent. Case VIII, aged thirty-five years, a questionable luetic infection, ten years before, untreated; for six months, loss of weight, increasing expectoration, recently sweats; right apex inactive lesion, left less extensive but active and with rales; numerous mucous patches; Wassermann, von Pirquet, tubercle bacilli, all positive: salvarsan (0.5), in six hours slight pulmonary focal reaction, increasing expectoration and very slight fever, followed by prompt general and local improvement, one month later acute bronchitis, but improvement persisted, and weight increased. Case IX, aged twenty-nine years, lues for eight years, four inunction cures; double apical catarrh; Wassermann and von Pirquet positive, tubercle bacilli negative; salvarsan (0.6) without reaction, increase in weight. Case X, aged thirty years, lues three years previously, four inunction cures; cough for three years, change of climate with benefit, for two months worse, cough increasing, expectoration frequently bloody, loss of strength, sweats; right apex active process with rales, left inactive, left cervical glands below jaw enlarged; Wassermann, von Pirquet, positive, bacilli in sputum: salvarsan (0.6), in six hours, slight focal reaction, and slight increase in expectoration, five days later, glands still more enlarged, fever, latter disappeared after extraction of teeth; eleven days later: salvarsan repeated, slight transitory hemoptysis and fever; twenty-four days after salvarsan, sudden marked enlargement of glands, fever, dyspnea, operation, no reaction (glands not examined microscopically): salvarsan (0.3) twice in one month,

very slight focal reaction, marked improvement, tubercle bacilli and rales disappeared. Case XI, aged thirty-two years, fourteen years before, a questionable luetic infection untreated for past year, cough, gradually increasing expectoration, sweats, loss of strength, last few weeks hoarseness; right, active lesion with rales; left, inactive; left vocal cord inflamed and covered with secretion; Wassermann, von Pirquet, tubercle bacilli, all positive: tuberculin emulsion, general improvement, but lungs did not clear up and rales appeared at left apex: salvarsan (0.6), followed by a marked pulmonary focal reaction and slight transient fever, and then lungs became drier; three weeks later: salvarsan (0.4) followed by same reaction; three weeks later, decided diminution of rales, marked improvement in vocal cord, discharged with few bacilli in sputum, weight much increased. Case XII, aged twenty-eight years, eight years before, a suspicious primary sore but no treatment; for two years, cough, bloody expectoration, sweats; improved at hospital, relapse with loss of strength, chest pain, cough, expectoration, sweats; double apical lesion, rather extensive, right with rales; Wassermann, von Pirquet, tubercle bacilli, all positive; gradual increase and extension of the process and lighting up of activity at left: salvarsan (0.3), six hours later, transitory, pronounced; focal but no general reaction nor fever, weight increased, general but no local improvement till four months later.

These excellent results were, to be sure, obtained in patients under careful observation and under sanatorium treatment. The lapse of time intervening between the treatment administered and the writing of the report is, of course, relatively short for a critical judgment upon patients with so chronic a disease as tuberculosis.

Jeanselme, Vernes, and Bloch,[32] influenced by the frequently unfavorable effect of mercury upon patients with tuberculosis, by the well-known utility of any form of arsenic against tuberculosis, by the stimulating action of salvarsan upon the blood-making organs and upon general nutrition, and not intimidated by the possibility of awakening a dangerous congestive reaction in pulmonary lesions by the intense vasomotor effect of the new drug, followed for three years the effect of salvarsan or neosalvarsan upon 13 patients with combined syphilis and tuberculosis. In 5 advanced cases no benefit was noted upon either the general or the local condition; but no aggravation was produced. From the authors' description it is very questionable whether or no the treatment employed produced "no aggravation," just as it is difficult to understand why they chose three such cases as I, III and V without any evidence of active lues except a positive Wassermann in the last mentioned, and yet all so manifestly clinical problems in advanced stages of tuberculosis. The doses employed in Case I

[32] Bull. et mém. Soc. méd. d. hôp. de Paris, Series 3, 1914, xxxvii, 340.

were too large and certainly in Case V the interval too brief. Although active syphilis co-existed in Cases II and IV, here too smaller doses and longer intervals would have been more appropriate in such serious and advanced tuberculous disease. The luetic infection was manifestly active, and the more striking clinical factor in the two cases next cited, with cavities or softening; but the beneficial effect of the drug, though apparent, was only transitory. The doses selected were more appropriate but could well have been smaller, and the interval in Case VII was too brief. Their most encouraging results were noted in the 6 following cases: Case VIII, aged thirty-five years, ulcerating syphilide, infection three years previous, Wassermann positive; both apices, scattered consolidation, recently a profuse hemoptysis, two series of "hectine" (0.1), poorly tolerated, but syphilitic lesions cicatrized, Wassermann still positive: salvarsan 0.5, 0.12, 0.2 four times from September 2 to December 6, 1911; no ill effect, increasing weight, general improvement: 0.25 repeated five times from December 9 to January 6, 1912: 0.25 followed by 0.3 four times from February 14 to March 19, 1912: discharged in April, condition excellent, no further hemoptysis, gradual fall of temperature, from between 37.2° and 38.8° before treatment to 37° after first course, where it remained except for one brief rise. Case IX, aged twenty-three years, recurrent roseola, pale, puffy, weak, anemic, dyspneic; rough blowing expiration, at both apices: neosalvarsan (0.15), followed by 0.3 seven times from August 30 to October 7, 1913; increased weight, improved color, rapid general improvement: neosalvarsan 0.3, 0.6, and 0.75 four times, general condition excellent on February 20, 1914. Case X, aged 31 years, February, 1913, secondary syphilis; for past two months, cough, expectoration, fever, sweats, loss of weight; both apices slightly dull, right rough cog-wheel inspiration and crackling rales: salvarsan, 0.15 three doses, 0.2 and 0.25 twice from February 18 to March 25, 1913, fever and sweats ceased, general improvement. Case XI, aged forty-five years, September, 1912, roseola, Wassermann positive, tuberculosis for six years; at entrance nauseating cough, bloody sputum, night sweats, emaciated, dysenteric enteritis; right apex, slight dulness, rough breathing and crackling rales; previously received fifteen injections of biniodide, followed by paroxysms of suffocation, nauseating cough and bloody sputum: salvarsan, 0.3, 0.35, 0.4, four times from October 15 to November 19, 1912, vomiting subsequent to first doses, otherwise steady improvement; March 3, 1913, cough and active signs in chest disappeared, Wassermann negative; July 2, general condition excellent, gain in weight, rough respiration at left apex; February 16, 1914, general condition good, slight dulness and few subcrepitant rales at left apex. Case XII, aged twenty-eight years, epididymitis, extensive perforation of palate, destruction of pillars and

uvula, weakness, extreme pallor, night sweats, marked emaciation; right apex, rough blowing respiration: salvarsan, 0.3 twice, 0.4 four times from October 8 to November 12, 1912; after third dose rapid improvement, gain in weight, cicatrization of palate, pulmonary signs without change. Case XIII, aged fifty-two years, buccal leucoplakia, typically fissured tongue, positive Wassermann, cough, hemoptysis, emaciation, anemia, fever, night sweats; dulness at both apices especially right, rough breathing, moist rales, nummular sputum loaded with tubercle bacilli; two days previously, two very profuse hemoptyses: salvarsan, 0.3 six times during December, 1911, and January, 1912; no further hemoptysis, fewer rales, fever and cough disappearing, better color, weight increasing, rapid general improvement, resumed work; December, 1912, left pleurisy, sick three months; October, 1913, loss of weight, fatigue, pallor, bacilli in sputum; apices, rough interrupted breathing but no rales; marked enlargement of tail of left epididymis and induration of vesiculæ, abundant mucopurulent uretheral discharge, appearing suddenly but painless: salvarsan 0.15, 0.2, 0.25, neosalvarsan 0.45, 0.65, 0.6 twice during December, 1913, and January, 1914; general improvement, increase of weight and color, no pulmonary setback.

The doses employed in these six cases, all very much less acute and advanced than in the first two groups, were more appropriate; certainly the results were more striking. Following the discussion of their report, Renon illustrated the harmlessness of and the excellent toleration to the drug in two similar patients, to whom he administered 0.15 and 0.2, and in four patients with uncomplicated tuberculosis who tolerated perfectly 0.1 to 0.15; but, in the latter, no specific action of the drug upon the tuberculous process could be detected. Belin tried salvarsan upon several patients with definite tuberculosis and recent secondary lues; both diseases always improved and in two instances were at least temporarily cured.

At Laennec Hospital, Bernard and Paraf[33] treated with salvarsan 9 patients with evidence both of tuberculosis and of syphilis. Of the 3 recently infected with the latter disease, 2 (Cases II and IV) had an active pulmonary process, the first dose of neosalvarsan was followed by a Herxheimer reaction, and in all three the antiluetic effect of the drug was rapid and excellent. A brief summary of their cases follows: Case I, aged twenty-six years, primary five years before, Wassermann positive, recent acute tuberculosis with softening and cavity formation, hemoptysis and anemia: successful artificial pneumothorax several times, later complete collapse; followed by seven doses of neosalvarsan (0.5 to 0.7) in three months; excellent result. Case II, aged twenty-

[33] Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, 3 s, xxxvii, 357.

eight years, early secondaries breaking out during a recent exacerbation of chronic phthisis with softening, cavity formation and bacilli: five doses of neosalvarsan (0.3 to 0.75) in five weeks; rapid improvement after third dose. Case III, aged thirty-nine years, cerebrospinal lues (tabetic) with positive blood and spinal fluid, fibroid phthisis, without demonstrated bacilli: seven doses of neosalvarsan in nine weeks (0.37 to 0.7); general improvement. Case IV, aged seventeen years, diffuse secondaries during tuberculous activity at one apex: four doses of neosalvarsan in three weeks; rapid disappearance of evidences of syphilis. Case V, aged forty-five years, lues twenty-two years before but without symptoms at time of observation, Wassermann positive; chronic tuberculous polyadenitis with suppuration: three doses of neosalvarsan without focal glandular reaction or any other recognizable effect. Case VI, aged forty-eight years, lues twenty-five years before with recent cerebrospinal involvement; advanced caseous pulmonary, renal, and bladder tuberculosis; seven doses of neosalvarsan (0.25 to 0.3); curative result upon syphilitic symptoms. Case VII, aged fifty-eight years, lues thirty years before, Wassermann positive; tuberculous ulcer of skin and fibroid phthisis: three doses of neosalvarsan (0.2 to 0.45) well borne. Case VIII, lues twenty-two years before, Wassermann positive; active fibroid phthisis: three doses of neosalvarsan (0.3 to 0.6) in three weeks, well borne three and a half weeks later; Wassermann negative. Case IX, aged thirty years, lues recent, profuse hemoptysis following prolonged course of mercury, six months later, pleurisy following more mercury: series of neosalvarsan well borne.

They conclude that the existence of pulmonary tuberculosis offers no special drawback to the proper administration of salvarsan; believe in the selection of moderate or small doses especially in cachectic cases with advanced lesions; emphasize the excellent results obtained upon the syphilitic manifestations and upon the general condition, as well as the perfect tolerance of patients with chronic tuberculous lesions even when advanced, progressing or combined with cachexia; but they failed to note any beneficial effect upon the actual tuberculosis. They did not employ the drug in acute tuberculosis. Sergent's experience mentioned in the discussion of their report confirmed all their conclusions.

Blinder[34] cites the case of an alcoholic with a positive Wassermann, a history of gonorrhea at sixteen years, of influenza and a fistula in ano two years before, and with a sudden onset of pulmonary symptoms and signs but without bacilli in sputum. Mercury and iodide of potash were followed by pronounced general and pulmonary benefit; salvarsan (0.6) expedited the cure. Hartley[35] tried neosalvarsan in 16 patients with tuberculosis at varied

[34] Med. Rec., New York, 1914, lxxxvi, 330.
[35] Lancet, London, 1914, i, 1602.

stages (only 1 of which was proved to be combined with lues) and in 14 obtained improvement. In nearly all of them its effect was especially striking in reducing the pyrexia which had resisted all the usual measures previously employed. He acknowledges that the rest and favorable surroundings may have been important factors. He cites 4 illustrative cases with temperature charts. The latter suggestively support his belief in the antipyretic and general beneficial effect of the drug. The proved luetic patient was a male, aged thirty-one years, with a severe cough dating back five months, emaciation, night sweats, afternoon temperature of from 99.2° to 101.6°; consolidation of both apices and of upper part of right lower and excavation of right apex; profuse expectoration with only a few bacilli after several fruitless searches; extreme hoarseness, a luetic laryngitis, and a markedly positive Wassermann; the fever persisted despite rest and the usual hygienic measures: neosalvarsan 0.9 followed only by malaise, in seven days temperature normal but rose again: neosalvarsan 0.9, salvarsan 0.4 (Joha, intramuscular), and neosalvarsan 0.9, discharged markedly improved in every way and with a negative Wassermann but without change in the pulmonary signs.

By far the largest group of cases has been recently reported by Fagiuoli[36] from M. Ascoli's Pathological Institute at Catania, and the treatment was so carefully and systematically carried out that a brief summary of the cases is included in this review. His material was collected during four years at the Ferrarotto Sanatorium, where he found lues in 60 to 65 per cent. of the male patients with tuberculosis. He usually selected neosalvarsan, began with 0.1, increased only 0.1 or at most 0.2 each time, and gave four or five consecutive doses. Most of his patients also received several intramuscular injections of calomel either some time before the administration of salvarsan or after the completion of one or more series of injections of the latter, and its effect was generally striking and very encouraging. The majority had the benefit of sanatorium and climatic treatment as well. Case I, aged twenty-three years, for one month, persistent cough with profuse mucopurulent expectoration, pains in right chest, constant headache, anorexia, insomnia, general weakness, temperature 37.5° to 38°, lost 6 kilos.; left apex rough breathing, right, few dry rales; right subspinous and base rales, no bacilli, von Pirquet negative: general treatment; ten days later, roseola, hoarseness, mucous patches, Wassermann positive, confessed infection two or three months before: neosalvarsan 0.1, 0.2, 0.3, 0.5, then calomel 0.1 three times; complete cure, Wassermann negative; two years later, condition excellent. Case II, aged twenty-four years, lues one year previously: calomel three injections, prompt cure; one month later, increasing cough

[36] Ann. di Clin. Med., Palermo, 1915, vi, 23.

and sputum, intense headache, gastro-intestinal disturbance, slightly dysphagic, general weakness, loss of weight, occasional fever, no bacilli; no benefit from general treatment; sputum became pinkish; diffuse rales mostly at right base and right mid lobe; general adenitis, pharyngitis, mucous plaques; Wassermann positive, von Pirquet negative: calomel 0.5 six times, neosalvarsan 0.2, 0.3, excellent result. Case III, aged twenty-nine years, lues at twenty-four, cured with calomel; one and one-half years later, morning cough, dry, then with mucopurulent expectoration, no bacilli, hoarseness, anorexia, weakness, anemia, no fever: general and climatic treatment; six months later, much better except cough; one year later, return of above symptoms with fever, increasing laryngeal catarrh, no bacilli, von Pirquet negative, but diagnosed as pulmonary tuberculosis; rough inspiration and few rales right apex anteriorly, and at left and right apices posteriorly, still more rales at left base: climatic treatment till April, 1913; one and one-half years later, increased cough and persistent sputum, 125 to 150 grams daily, laryngitis, fever, general symptoms and chest pains, chest signs same, no bacilli, rash, confessed lues, Wassermann positive: calomel plus neosalvarsan 0.1, 0.2, 0.3, 0.5, marked improvement first on rash, larynx, general condition, cough, expectoration; increasing weight, finally only slight morning cough and few rales left.

In the next six cases, plainly predisposed to tuberculosis, the luetic infection evidently activated a latent pulmonary focus, which, except in Case X, broke out within two years of the onset of the specific disease. Although prompt and vigorous antisyphilitic treatment is usually a distinct help to combat such an awakening of tuberculosis, some of these patients obtained little, and others, no apparent benefit.

Case IV, aged twenty-six years; mother died of phthisis; at sixteen years, bronchial catarrh cured in a few months; lues, 1912, no treatment, no signs; in May, dry cough, then with mucopurulent sputum, anorexia, weakness, emaciation, sweats, fever, headache, bacilli; in July at sanatorium, bronchopneumonia of right upper and middle lobes, rales left apex, Wassermann positive: neosalvarsan 0.1, 0.3, 0.4, 0.5; good general and pulmonary effect but Wassermann still positive; January, 1913, pulmonary signs unchanged, increasing general symptoms, mucous patches: neosalvarsan 0.4, 0.5; calomel 0.5 four times; improvement decided, Wassermann negative, condition remained excellent. Case V, aged twenty-one years: father luetic, died of phthisis; numerous attacks of bronchial catarrh, alcoholic; lues March, 1910, in three months secondaries: few injections mercury iodide; one year later, cough, mucopurulent sputum, anorexia, weakness, emaciation, anemia, slight fever, severe hemoptysis, bacilli; sanatorium, October, 1911; diffuse bronchopneumonia with cavity formation

entire right chest, Wassermann positive: neosalvarsan 0.35: calomel 0.1, four times; slight general improvement, no pulmonary change; artificial pneumothorax, with excellent effect and left sanatorium March, 1913; calomel six times, very little cough, no signs of lues, remained well. Case VI, aged twenty-six years; mother died of phthisis; patient in excellent health, robust, tubercle bacilli in blood (?); February, 1912, without symptoms or signs, von Pirquet slightly positive; one year later lues: mercury iodide, twenty times; four months later, exudative pleurisy left chest, very severe and prolonged, fever high, chest tapped twice, bacilli in serum, increasing cough with sputum but without bacilli and no signs of pulmonary consolidation; left hospital, but weakness, anorexia, and cough persisted, fever recurred, sputum pinkish, bacilli; rales at right apex and base, pulmonary process extensive and diffuse, nutrition very poor, Wassermann positive: neosalvarsan 0.1 to 0.5, five times; slight benefit in general condition, transitory tendency to arrest; following hemoptysis, an extension of process. Case VII, aged thirty years; in childhood, cervical adenitis and operation; at nineteen years, bronchial catarrh for several months, cured; March, 1912, sanatorium, lues five months before; two months later, severe rapid phthisis; diffuse bronchopneumonia left, slight process with rales right apex, bacilli; Wassermann positive, enlarged glands, roseola: neosalvarsan 0.1 to 0.5, five times, with excellent result both pulmonary and general; Wassermann negative; September, 1912, left sanatorium, went to the country and worked; signs very slight; one year later, calomel eight times, recently Wassermann negative, excellent condition except for few rales; no signs of syphilis. Case VIII, aged twenty years; father died of phthisis; at twelve years exudative pleurisy, cured in two months; at eighteen, lues; two months later, secondaries: mercury iodide thirty times; cured except for chronic laryngitis; two years later, cough, mucopurulent sputum, chest pains, sweats, increasing weakness, emaciation, laryngitis worse, dysphagia, aphonia, dyspnea; sanatorium; three months later, in wretched condition; rales and rough breathing at right apex, bacilli; Wassermann positive: neosalvarsan 0.1 to 0.5, five times, larynx benefited first, ulcers cicatrized, increasing weight and general improvement; one year later: calomel 0.5 four times and mercury iodide thirty times; left sanitorium, Wassermann negative, no bacilli, only slight cough and few rales. Case IX, aged thirty years; mother and brother died of phthisis; in youth, for several months, bronchial catarrh; at sixteen, prolonged typhoid with pulmonary symptoms; at twenty-five, pleuropneumonia, two months in hospital; November, 1911, lues; three months later, secondaries, increasing cough, mucopurulent sputum, diffuse chest pains, weakness, anorexia, emaciation, sweats: calomel three times, and few inunctions of mercury; syphilis cured, general condition improved

but cough increased with mucopurulent occasionally pinkish sputum; still worked; January, 1912, sudden hemoptysis, bacilli; in March, sanatorium; diffuse bronchopneumonia, consolidation with cavity, at left, rales at right apex; Wassermann positive, mucous patches: neosalvarsan 0.1 to 0.6, five times; lues cured, pulmonary signs arrested; general condition improved: tuberculin; March, 1913, signs much improved, left sanatorium, did not follow advice, returned in a few months and died. Case X, aged thirty-eight years; father died of phthisis; at twenty-one left exudative pleurisy, three months in hospital; at twenty-seven, lues: calomel eight times and several inunctions of mercury; cough, mucopurulent sputum; both disappeared in a few months; at thirty-five years, February, 1912, gumma in nose, ulceration and necrosis of bone; bronchopneumonia; two months in bed: neosalvarsan once, nose began to improve, also pulmonary process; left hospital with cough, chest pains, mucopurulent sputum, occasional slight fever; later, general weakness; returned for few months; bacilli; diffuse bronchopneumonia at left, rales at right apex; Wassermann negative, luetin positive: neosalvarsan, increasing doses five times; calomel, 0.5, three times, marked general improvement but no change in lungs.

When lues is acquired by patients in poor general condition with severe and diffuse pulmonary tuberculosis, and with other organs affected, nearly all of them do badly. Under such conditions antiluetic treatment, even if active and prompt, will be of little or no benefit, as is well illustrated by two of the next three cases:

Case XI, aged twenty-nine years. February, 1910, severe hemoptysis, followed by pulmonary symptoms; sanatorium, August, 1911, condition grave, fever; in both chests diffuse bronchopneumonia, cavity formation right; four months' treatment at sanatorium with diminishing fever, but no change in pulmonary signs; worked one year in this condition; January, 1913, lues and secondaries: calomel, 0.2, four times, improved the luetic symptoms but general condition, already serious, became much worse; sanatorium in April in very bad condition, with fever and cough; Wassermann negative: neosalvarsan 0.1, 0.3, 0.4, without effect, died. Case XII, aged thirty-five years, cough, mucopurulent sputum, chest pains, sweats, anorexia, weakness, wretched nutrition, and grave general condition for two years; diffuse bronchopneumonia, rales at right apex, rough breathing left; sanatorium, March to July, 1912, without improvement; lues in December: neosalvarsan, given once intramuscularly; calomel 0.5, three times; three months later, marked aggravation in cough, sputum, dyspnea, and fever; sanatorium, April, 1913, both sides now diffuse pulmonary process with cavity formation right; Wassermann positive: neosalvarsan, three times, brief general improvement, then severe hemoptysis, rapid aggravation, died. Case XIII, aged twenty-five years, 1909, phthisis, slowly advanced; sanatorium

April, 1911; fever, diffuse bronchopneumonia at left, slight process with rales right apex, adhesions prevented artificial pneumothorax; general condition improved, no change in pulmonary condition, resumed work in September; lues in December; one month later, afternoon fever, increasing cough and expectoration; sanatorium, February, 1913, chest same; Wassermann positive: neosalvarsan, 0.1 to 0.5, five times, general as well as a gradual improvement in pulmonary condition; May, 1913, tuberculin; February, 1914: neosalvarsan three times; now in excellent condition, no signs of syphilis, Wassermann negative, chest signs much improved.

The luetic infection in Cases XI and XII aggravated both local and general condition and contributed to the fatal issue. The relatively good condition of Case XIII, at the onset of lues, favored the treatment and therefore improvement eventually resulted.

When a tuberculous lesion is of limited extent, well localized and advancing slowly, the acquisition of lues would seem almost to render the bacillary disease less serious, at least after subsidence of the initial acute symptoms. Antiluetic treatment assists; but the final result depends upon the tuberculous process itself and its appropriate treatment:

Case XIV, aged twenty-nine years; mother died of phthisis; 1907, cough, sputum, pains in chest, anorexia, weakness, fever, bacilli: to country; one year later, general improvement, only occasional cough and slight sputum, bacilli few; diffuse but slight pulmonary signs; worked three years, in good general condition, same few signs in chest; February, 1911, lues: mercury iodide; syphilis improved, but general condition became aggravated, cough increased, sputum, fever, weakness, emaciation; September, severe hemoptysis; October, sanatorium; diffuse bronchopneumonia right chest, rales left apex; Wassermann positive: neosalvarsan, five times, with gradual improvement; chest signs much diminished, Wassermann slightly positive; April, 1913, discharged; in winter: calomel 0.5, eight times; signs very slight, bacilli very rare, Wassermann negative. Case XV, aged twenty-eight years, hemoptysis at fifteen; February, 1911, sanatorium, slight fever; bronchopneumonia upper and mid right, apical catarrh left; in winter, cough, sputum, slight fever, general improvement, signs unchanged, worked about one year, condition remained same; January, 1913; lues, much worse, increasing cough, slight dyspnea, anemia, weakness, emaciation, fever: calomel 0.5, seven times, better, chest same, Wassermann positive; August, secondaries, respiratory symptoms increased, profuse hemoptysis, very severe anemia and poor general condition; diffuse bronchopneumonia entire right chest, slight activity left apex, Wassermann positive: neosalvarsan, increasing doses, four times, general improvement, but fever and signs persisted; December, neosalvarsan, 0.3 twice, 0.5, with prompt decided improvement; tuberculin, condition continued

to improve, Wassermann negative, signs less diffuse and less marked. Case XVI, aged thirty-five years, phthisis at twenty years, slight hemoptysis, four or five times; in hospital few months, condition very grave, then worked with only slight cough and sputum; at twenty-six, lues with secondaries and exacerbation of other symptoms: calomel and mercury inunctions; pulmonary condition worse; readmitted: general treatment, improvement resulted, worked with only cough; November, 1912, gumma, general condition much worse, cough, sputum, fever, bacilli, Wassermann positive: salvarsan 0.5; calomel 0.5, four times, with considerable improvement, except pulmonary signs, then artificial pneumothorax with excellent result, Wassermann negative. Case XVII, aged twenty-nine years, summer of 1911, slight hemoptysis, alcoholic, bad hygiene but general condition same till September, 1911, when received a blow in right chest with pain, respiratory disturbance, fever; bronchopneumonia in right upper chest, exudative pleurisy left: tapped, improved, worked; March, 1912, lues, no treatment, respiratory disturbance increased after few months; sanatorium, grave condition; diffuse consolidation entire left chest, slight activity at right apex; Wassermann positive, hemoptysis: neosalvarsan, 0.1 to 0.5, five times, improvement but not rapid; October, rash, mucous patches, headache: neosalvarsan twice; calomel 0.5, four times, slow improvement in luetic also in pulmonary symptoms; left sanatorium, Wassermann positive, signs less, poor hygiene but worked one year with little change in condition; winter 1913–1914, exacerbation and death following acute alcoholism.

The next case illustrates the sclerotic effect which, after the preliminary activity has ceased, follows the luetic infection and is actually beneficial as has been so frequently emphasized by E. Sergent.[37]

Case XVIII, aged twenty-six years, double pneumonia at fourteen years, alcoholic and bad hygiene but well and strong till nineteen; 1907 phthisis, winter cough, mucopurulent sputum, bacilli, weakness, anorexia, frequent sweats: general treatment without improvement; September, 1911, general condition and nutrition fair; diffuse bronchopneumonia right chest, slight activity left apex; October, 1912, lues with early secondaries: calomel 0.4, three times, mercury cyanide, ten times; accentuation of pulmonary symptoms with slight fever and subsequent hemoptysis: to country, remained in bed and improved; March, 1914, signs much less, few rales right, excellent general condition, Wassermann positive: neosalvarsan, 0.1 to 0.5, five times, marked improvement bacilli very rare, still further dryness at apices. The author, however, attributes the benefit obtained by this patient, largely to climatic and general measures.

[37] Syphilis et Tuberculose, Paris, 1907.

The next case illustrates how virulent the luetic virus may be:

Case XIX, aged twenty-two years, left exudative pleurisy with good recovery, except for cough, later with sputum; February, 1912, rales at right apex, bacilli very rare; toward end of 1912, lues, increasing respiratory symptoms, fever, became worse: calomel, 0.5, seven times; syphilitic symptoms cured, general condition poor; five weeks later, general eruption: salvarsan 0.5, rash disappeared; but tuberculous lesions spread and patient died in two months.

The remaining 4 cases illustrate the grafting of a tuberculous infection upon tertiary luetic lesions of the larynx or lung, and confirm Sergent's claim that the election of this sclerotic soil favors a chronic course or cure of the secondary invader. Antiluetic treatment exerted a favorable influence upon all; but, coinciding with the outbreak of gummata, XXI and XXII showed a temporary aggravation, both local and general:

Case XX, aged thirty-eight years, lues at seventeen years; mercury iodide, forty times in two successive years, no symptoms except laryngitis; six years later, cough, sputum, sweats, slight fever, bacilli in sputum, but worked in good general condition; sanatorium in winter of 1910; bronchopneumonia right upper and middle, slight at left apex; one year later, left sanatorium much improved; three months later, increasing laryngitis with fever; returned April, 1911, with same signs, aphonia, dysphagia, dyspnea, ulcerative laryngitis; Wassermann positive: local treatment without benefit: neosalvarsan, 0.1 to 0.5, five times; in four months, laryngitis gradually cured, symptoms in lungs improved: tuberculin; February, 1913: neosalvarsan, 0.2 to 0.4, three times; left sanatorium March, 1913, cured, without sputum, very marked improvement in signs, Wassermann negative; continued well.

Case XXI, aged forty-four years, lues at nineteen years: treated with mercury, no symptoms, except child died in early infancy, until at thirty-two years, gumma: calomel four times; at thirty-six, cough, slight bloody sputum, bacilli very few, worked; at forty, laryngeal catarrh and gumma, respiratory symptoms increased, slight hemoptysis, failure in general condition; sanatorium 1912; bronchopneumonia diffuse right, inactive left apex, bacilli positive, Wassermann positive: neosalvarsan, 0.1 to 0.5, five times, improvement prompt in luetic symptoms, gradual in pulmonary and general condition; discharged; April, 1913, signs less, bacilli few, Wassermann negative; continued improvement.

Case XXII, aged fifty years, lues at twenty-two, secondaries late: few mercury injections and inunctions, cured; alcoholic, poor hygiene yet well till forty when had several hemoptyses with fever, temperature normal in one month, but cough, mucopurulent occasional bloody sputum, anorexia, weakness persisted; hospital, bacilli, in two months improved, worked, only cough remained;

at forty-six, exudative pleurisy, increase in fever, tapped, condition serious; consolidation at both apices; general improvement for two years with only an occasional hemoptysis; November, 1912, diffuse pulmonary lesion, increasing cough, sputum, pain in chest, headache, fever, gumma, Wassermann negative, luetin positive: neosalvarsan, 0.1 to 0.6, six times; lues cured, signs and pulmonary symptoms improved; and retained improvement except cough and very slight hemoptysis. Case XXIII, aged thirty-six years, lues at twenty, without treatment or symptoms except slight hoarseness for two years; at twenty-eight, exudative pleurisy right, cured in one and one-half months; at thirty-three (1911), symptoms of phthisis, cough, mucopurulent sputum, bacilli, sweats, fever, hemoptysis twice; April, 1912, sanatorium, condition very serious, Wassermann positive; bronchopneumonia right middle and lower, apical catarrh left; two months later ulcer of larynx: local treatment without effect: neosalvarsan, 0.1 to 0.5, six times, marked improvement of larynx but none in other symptoms, left sanatorium one year later with fever and a very diffuse process; four months later died from hemoptysis. Case XXIV, aged forty-eight years, lues at twenty-five years, only slight treatment; at thirty-three years, gumma on forehead, disappeared without treatment; at thirty-nine years cough, sputum, pains in chest, fever, increasing weakness, emaciation, slight hemoptysis; hospital six months, bacilli, improved but sputum bloody; worked till February, 1912, then suffered a blow and had hemoptysis, anemia, increasing respiratory symptoms; sanatorium in July, in fair condition and nutrition; diffuse bronchopneumonia left, consolidation right lower; very slight headache, Wassermann negative, luetin positive: neosalvarsan, 0.1 to 0.5, five times, prompt improvement of specific, gradual of general symptoms, signs lessening in extent and degree.

Despite the serious general condition, and despite the very diffuse character of the pulmonary tuberculous lesions in many of the cases cited above, the author only once observed an intolerance to the drug; but neither a focal (tuberculin-like) reaction nor any phenomena of congestion. He also employed calomel freely and with no ill effect except upon two patients with intestinal disturbances and one with hemoptysis; he never employs iodide of potash because of the danger of reaction and congestion. Neither salvarsan nor neosalvarsan produced any improvement in a small series of strictly tuberculous patients (5 in the first, 2 in the second, and 2 in the third stages of pulmonary tuberculosis); and he further states that there is no evidence available which would lead one to expect any benefit from these arsenic derivatives unless syphilis co-exists. If antiluetic treatment be instituted in the early period of syphilization where a tuberculous infection already exists, a prompt recovery from the sudden insult occurs; and the individual regains or increases his powers of defense in the struggle against

the tuberculous germ which he also harbors. If, on the contrary, tuberculosis develops in an old syphilitic, antiluetic treatment will always benefit the syphilitic soil, upon which and on account of which the tuberculous process develops.

He further concludes as follows: (1) The association of lues and tuberculosis is much more frequent than usually credited; (2) lues offers a striking predisposition for tuberculosis; (3) their co-existence is not necessarily fatal and many cases recover; (4) the development of tuberculosis in primary lues is generally due to reawakening of a latent tuberculosis and is apt to run a severe course; (5) tuberculosis developing in old luetics runs a benign course and tends to sclerose; (6) lues, developing in active pulmonary tuberculosis, always aggravates the general and the local condition; although if the tuberculous process is limited and torpid this aggravation is apt to be transitory; but if the pulmonary lesions are diffuse and serious, a fatal result will inevitably follow; (7) every case demands vigorous antiluetic treatment; it is always well tolerated and frequently produces a favorable effect upon the tuberculous process.

Culver[38] has recently described the striking effect of one dose of neosalvarsan (0.45) followed by mixed treatment upon a case of probable pulmonary syphilis which closely simulated tuberculosis, although two examinations of sputum were negative. The signs and symptoms of tuberculosis were promptly cleared up by treatment. Pontano[39] reviews his experience with 500 injections of salvarsan and neosalvarsan in various types of lues and in a few non-luetic conditions. He treated, with 23 injections, eight patients with pulmonary syphilis, six of whom entered the hospital for hemoptysis and in only one of whom it persisted. He merely states without any details that the treatment produced a general improvement, with diminished headache and fever; but did not alter the amount of expectoration, the physical signs nor the amount of aereation of lung as judged by the radiograms. Fischer[40] recently reported several deaths following the use of salvarsan; and of these two were patients with tuberculosis. In one of them, besides an involvement of the lungs and ulcers in the intestines, the autopsy showed that both adrenals were caseated and nearly completely destroyed; so that although the color of the patient's skin evidently might have suggested Addison's disease and thus prevented the employment of the drug (two doses 0.4 and 0.5, seven days apart) death could have been but slightly hastened. To the other, a marked alcoholic, an initial dose of neosalvarsan (0.45) in addition to mercury was given on the day of entrance and both drugs were apparently well tolerated. Six days later, the neosalvarsan (0.6)

[38] Jour. Am. Med. Assn., Chicago, 1915, lxiv, 335.
[39] Policlinico, Rome, 1915, Sez. Medica, xxii, 145, 227.
[40] Deutsch. med. Wchnschr., 1915, xli, 908.

was repeated and the patient left the hospital. Four days after, he was brought back unconscious and in convulsions; the next day he died. Autopsy showed that death was probably caused by an acute alcoholic pneumonia, but also that he had an active and extensive pulmonary tuberculosis. The treatment was evidently injudicious. Chauffard and Le Conte[41] have quite recently reported an eruption of erythema nodosum which coincided with the appearance of early secondaries in a patient with syphilis and inactive tuberculosis (intense von Pirquet, radiogram revealing considerably enlarged mediastinal glands and consolidation in the upper left lobe). A series of injections of cyanide of mercury (fifteen doses of 0.01) was promptly followed by a disappearance of the erythema and a general improvement. Four weeks later a course of novarsénobenzol de Billon (0.15, 0.30, 0.45, 0.60, three times) was given intravenously from July 28 to September 5. After the first dose (0.6) the nodular erythema reappeared and became much intensified; to fade and disappear again within four days. The same nodular eruption reappeared though less vividly after the third and fourth doses (0.6); but only persisted three and two days respectively. They consider that the first outbreak of erythema was of a tuberculous origin, awakened by the incidence of the syphilitic infection, and they liken the reappearance of the eruption, following the larger doses of arsénobenzol to a sort of focal reaction, similar to that of tuberculin. Among 4000 routine tests upon hospital patients, Walker and Haller[42] found only three of the 90 cases of outspoken pulmonary tuberculosis with a positive Wassermann reaction. All the cases of tuberculous meningitis gave negative tests both in blood and spinal fluid. The pulmonary signs and symptoms of one case rapidly cleared up under salvarsan, mercury and potassium iodide.

Fordyce[43] states: "I have treated a number of syphilitic patients who had at the same time tuberculosis. I find that by giving them small doses not more than 0.2 or 0.25 gram, at intervals of from two to four weeks, that the salvarsan has apparently a tonic effect on the patient. Patients with tuberculosis who are given salvarsan in large doses at frequent intervals I have found to react badly to the drug."

Conclusions. 1. The prompt employment of salvarsan or neosalvarsan is indicated in latent, chronic and moderately active tuberculosis: (*a*) as soon as the nature of an added infection is diagnosed with reasonable probability to be syphilis; (*b*) whenever the history, signs, or symptoms strongly suggest a previous luetic infection, particularly if such a patient is not improving upon the usually successful hygienic and climatic treatment for tuberculosis;

[41] Annales de Médecine, 1915, ii, 563.
[42] Jour. Am. Med. Assn., Chicago, 1916, lxvi, 489.
[43] Personal communication.

but (*c*) active tuberculosis, acute tuberculosis, and diffuse miliary tuberculosis are usually definite contra-indications to the use of these new arsenic preparations; although in both the first two mentioned groups there will be found many luetic patients upon whom a small dose of salvarsan may well be tried and, unless followed by untoward effects, cautiously repeated in gradually increasing doses.

2. When tuberculosis infects or becomes active in a patient with secondary, tertiary or even latent syphilis, the careful employment of one of these drugs is also indicated.

3. The more active the tuberculosis, the smaller should be the initial dose; the slower its increase, the less frequent the interval, and the greater care and watchfulness required.

4. Tuberculin-like focal reactions may follow their administration, should be carefully watched for and if present, the location, intensity and character will frequently guide in the selection of the next appropriate dose or interval.

CLINICAL INVESTIGATIONS ON INTESTINAL AUTO-INTOXICATION, ESPECIALLY AS REGARDS THE QUESTION OF SPECIFICITY OF TOXIN.[1]

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We wish to present very briefly a few observations on the specificity of toxin or bacteria in certain cases of so-called intestinal toxemia or bacteriemia, not in an attempt to draw any definite conclusions from these observations, but rather to chronicle certain rather striking findings in the hope of stimulating discussion on this subject of so much interest and yet of such almost universal misconception. These cases, although few in number, were studied rather intensively in the hospital, where each was under careful observation for a period of at least four weeks; they comprised 3 cases of chronic eczema and urticaria, 1 of pruritus, 2 of so-called bilious headache, and one of choroiditis. The 3 cases of chronic extensive eczema with urticaria gave almost identical histories, the salient points of which were as follows:

Case I.—Young man, aged twenty-six years. Negative past history, except a little eczema all his life; hay fever every summer; an absolutely normal digestion before the present illness, except a slight tendency to constipation; rather nervous; moderate user of

[1] Read at the meeting of the Association of American Physicians, May, 1916.

alcohol and tobacco. Present illness began nine months before he was seen by us—eczema of the big toe, gradually spreading until it now involves the whole body; has had many treatments, but all unsuccessful. The salient points of the physical examination were a very extensive eczema, scaly or weeping, with also some definite urticaria, a normal blood count, except 12 per cent. of the eosinophiles and 46 per cent. of neutrophiles; test meal: free hydrochloric 10, total 15; stool cultures aërobic normal, anaërobic sterile; test meal on leaving hospital, normal (six weeks later).

Case II.—Man, aged fifty-four years. Absolutely negative family and past history; onset of present illness five months before, beginning on thighs, and now involving entire body, associated with attacks of urticaria and angioneurotic edema. Physical examination showed a moderately enlarged liver, a diffuse papular squamous eczema, with some urticaria, a normal blood count, the eosinophiles being but 2.5 per cent.; stool examination negative both as regards bacterial, chemical, and microscopic findings; test meal: free hydrochloric acid 18, total 30.

Case III.—Woman, aged forty years. Absolutely negative past history except tendency to constipation, with slight gastric indigestion. The patient had had a diffuse eczema with urticaria for over a year without definite cause. The physical examination showed this condition and was otherwise negative, except that the test meal showed a complete absence of free hydrochloric acid; the stool and the blood were normal.

Tests of cutaneous sensitiveness to proteins were made in all 3 cases by the method employed by Blackfan—milk, egg-white, horse serum, meat juice, and barley protein being employed. The first 2 cases showed marked hypersensitiveness to all the proteins, except that there was no reaction to egg-white in the second case and very slight in the first. The third case showed no cutaneous reaction to any of the proteins. In the first 2 cases a meat-free diet with no cereals brought about a rapid improvement leading to a permanent cure; in the third case the effects of such a diet were *nil*. In the first case, after two weeks of complete freedom from skin lesions, the giving of one egg reproduced within twenty-four hours the original cutaneous picture; but after another two weeks of meat-free diet, egg-white was given again in teaspoonful doses daily, gradually increased, subsequently feeding other proteins in a similar way, so that now his tolerance has been so increased that he is able to take eggs, milk, and simple meats in moderate amount with no ill effects. He as well as the second patient has now been entirely well for nearly a year.

The case of pruritus was most interesting in many respects. The patient was a very nervous woman with a negative past history, except for several mild abdominal attacks suggestive of appendicitis, and also the history of chronic constipation. The physical exami-

nation showed marked cecal stasis, with slight tenderness on deep palpation, verified fluoroscopically as being due to a chronic appendicitis. The pruritus, which was general, followed directly upon an acute attack of indigestion, about eight months previous to her visit to us, which seemed to be referable to eating crabs and milk, and had continued ever since, although markedly aggravated by excitement and worry, and alleviated by the simple life. The gastric examination showed a true achylia, the stool cultures were negative, while her protein sensitization test showed a marked reaction with milk, but none with the other proteins employed. On a low protein diet, practically meat-free, with milk entirely eliminated, and the administration of hydrochloric acid and attention to the constipation, the pruritus gradually disappeared, and has now been absent for more than a year, while the study of her gastric contents shows a return of hydrochloric acid, though still distinctly subnormal.

The 2 cases of bilious headache had practically identical histories —chronic constipation associated with periodical attacks of severe headache associated with an increase in constipation, nausea, and vomiting, and always relieved by free purgation, especially by calomel and salts. Each showed a complete absence of hydrochloric acid in the gastric contents, no hypersensitiveness to the protein substances employed, each was markedly relieved by a diet from which animal protein food was practically eliminated, and in each an increase in the bowel sluggishness, a typical bilious headache, and, what was most interesting, a temporary but marked increase in the size of the liver could be brought about by giving meat for a short period of time.

The last case was perhaps the most interesting of all, for this was the only one of our series in which the bacteriological study of the stool gave pathological findings. This patient had recurring attacks of choroiditis, always preceded by digestive disturbances.

Case IV.—A young woman, aged twenty-seven years. Had typhoid fever at eighteen years, chronically constipated for about thirteen years, necessitating the constant use of purgatives, while the present illness was simply a continuation of her old history of constipation, although getting gradually worse with weakness, gastric and intestinal indigestion, pain in the stomach and in the lower abdomen shortly after eating, not related to the menstrual function, with, for the past four years, attacks of eye-ache and recently distinct impairment of vision. The physical examination showed a marked visceroptosis, with a maximum degree of cecal stasis, and fluoroscopic evidence of chronic appendicitis, a negative Wassermann reaction, a moderate anemia, practically normal gastric contents, the typical ophthalmoscopic picture of repeated attacks of choroiditis with old, black hemorrhagic deposits, while the stool examinations, of which twenty-six were made in conjunction with Dr. Sylvester, at the Woman's Hospital, showed when

the stool was acid nothing especially characteristic except occasionally a very few anaërobes, while with an alkaline stool the predominating organism was a large diplococcus, anaërobic, Gram-negative, with quite a number of a large and a small Gram-negative anaërobic bacillus.

The striking features of this case were (1) the apparently definite connection between the acute intestinal disturbances and the "eye-aches" of the patient, ophthalmoscopically recognized as acute attacks of choroiditis; (2) the fact that with these attacks the stools were always alkaline, while bacteriologically there appeared as the predominant microbes three Gram-negative anaërobes which we were unable to definitely identify, notably a large diplococcus, these anaërobes usually being practically absent when the stool was acid, while the diplococcus was isolated in pure culture from the appendix at the time of an appendicostomy operation performed later; (3) the extreme difficulty in keeping the stool acid even with a meat-free carbohydrate-rich diet, and enormous doses of an acid-forming bacillus—the Bacillus bulgaricus; (4) the considerable improvement brought about by a low protein diet, which was markedly increased by an appendicostomy with colonic irrigation through the new opening; (5) our ability to prophesy the choroidal attacks from the alkalinity of the stool and its large content in certain anaërobic bacteria.

When we speak of toxic symptoms we are unquestionably treading on debatable ground, and yet certain of the symptoms met with in these cases are explicable only on this basis. What is the cause of these toxic symptoms? Is it a toxin normally present or in excess? Has the protective mechanism become insufficient possibly due to repeated mild anaphylactic reactions, or is there a tendency toward an overgrowth of certain bacteria, notably proteolytic anaërobes, and may immunity be brought about in time? Whether these toxins are derivatives of the amino-acids we cannot say, but it is striking what slight changes in molecular constitution are necessary to convert the normal bases into products of great toxicity, and it is certainly possible that this may be brought about by the proteolytic intestinal bacteria. The work of Eppinger and Guttman in isolating two ptomains from the stool, one producing urticaria, the other asthma, is extremely suggestive in this connection. Whether these toxic anaërobes are always present in minimal amount, or whether they originate from external sources, such as tainted meat or pyorrheal pockets, has not been determined. That the poisons, produced by these bacteria or due to other causes, cannot often be demonstrated is not so much a proof of their absence as of their extreme complexity, and of the minimal amounts in which they must be present in urine, blood, and stool. The mechanical and surgical conceptions of intestinal stasis are quite insufficient to explain the symptom-complex presented. Back of

the mechanics of digestion lies a problem far more complicated, far more difficult to solve, the problem of congenital or acquired hypersensibility to certain stimuli, the question of the overproduction of certain toxic substances, their chemical nature, and their possible specificity, and various questions involving more definitely physical factors, notably absorption and osmosis.

In our series it is hard to escape the conclusion that in the intestine certain substances are produced which in some instances are possessed of specific action associated with a hypersensitiveness to certain proteins not in themselves toxic but possibly capable of producing a reaction because of an acquired hypersensibility, and that therapeutically a marked improvement in symptoms and even a complete cure may be brought about by the elimination of these substances from the dietary. It is also suggested by a study of these cases that by giving these foods in gradually increasing amounts a marked increase in resistance may be produced. That in certain cases at least the symptoms are better explained on the basis of a bacterial infection of intestinal origin rather than upon that of a toxemia, and that in various cutaneous lesions, testing the cutaneous sensibility by intradermal injection of various proteins is of real value in determining whether or not the condition may be due to certain toxic bases of intestinal origin derived from the decomposition of certain protein foods. These reactions are apparently specific in character, that is, are only found to be present when the toxins produced have a specific effect upon the skin, and therefore these tests of cutaneous hypersensiveness to various proteins probably cannot be used as criteria of other conditions best interpreted as protein intoxications with manifestations elsewhere than in the skin.

STOCK-BRAINEDNESS, THE CAUSATIVE FACTOR IN THE SO-CALLED "CROSSED APHASIAS."

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"La théorie de la gaucherie cérébrale, pleine d'obscurités, contredite par les faits, ne peut servir à expliquer pour les partisans du centre de Broca les destructions de ce centre sans aphasie."[1]

These words by Pierre Marie and his colleague Moutier, eight years ago, largely formed the basis of a momentous attack on the classical opinions concerning the positions of the centers governing

[1] L'Aphasie de Broca., Moutier, 1908, p. 127.

the functions of speech. As a result of this first onslaught the iconoclasts won for their objections a wide hearing and many disciples, whose ardor has since been somewhat cooled as much by the lapse of time as by the mobilization of the forces of the classicists. Nevertheless, as a result of these dialectics, the whole subject of the causation of the aphasias has been shaken, and not a few of us have failed to decide for ourselves as to the validity of the evidences adduced on both sides.

The cause of this indecision lies in the fact that apparently irrefragible evidence can be produced by both protagonists: by Moutier, for example, the case of Levi,[2] in which Broca's area was destroyed by neoplasm in a right-handed man without any aphasic symptoms having been produced; and, again, the experiments by Burckhardt,[3] who removed from two right-handed dements the foot of the third left frontal convolution without producing the least trace of motor aphasia in either subject.

It may be mentioned here that slowly growing growths destroying the speech area, as in Levi's and Collier's cases,[4] should not be comparable in effects with sudden lesions.

Opposed to these contentions, however, is a vast number of cases, the majority of which have been carefully observed; for instance, the first cases recorded by Broca himself, in which there was complete motor aphasia due to a hemorrhagic cyst in the posterior third of the second and third frontal convolutions; an even more important case than this is that of Simon, in whom a complete inability to communicate except by signs was instantly induced by the traumatic destruction of the left third frontal convolution.

It is not necessary to expand here the number of apparently indubitable cases capable of being cited both for and against the idea that Broca's area is in right-handed persons the brain center specialized for the government of the function of motor speech. It suffices to say that there lay to the hands of Marie and Moutier much evidence which bore heavily against the topographical notions then prevalent, and to remind ourselves that Moutier cites freely cases of right-handed right hemiplegics without aphasia and also cases of left-handed left hemiplegics without any disturbance of their power to converse. Further, the strongest evidence at Moutier's disposal consists of certain patients who might be called, in Bramwell's phrase, cases of crossed aphasia—eccentric combinations of right hemiplegia with aphasia in left-handed individuals, or left-sided palsy with aphasia in right-handed persons.

These cases were used by Moutier to disprove the validity of Broca's area as a special speech center, but in reality, as shall be suggested later, they only impugned the theory of constant con-

[2] Loc. cit., p. 102.
[3] Loc. cit., p. 103.
[4] Collier, Lancet, 1899, p. 824.

junction in any one subject of right-brainedness and left-handedness or left-brainedness and right-handedness.

To account for these anomalies there was born of Marie and Moutier the idea that not the area of Broca but the much wider lenticular zone was responsible for language control; a proper scorn is thrown on the clinician who, confronted by a third left frontal convolution destruction in a patient who in life had never been aphasic, falls back feebly on the theory that the said patient must have been left-handed either without self-knowledge of the fact or at least without its discovery by others. However, a language center or intelligence center postulated in the lenticular zone still does not rid us of the difficulty, more especially if the said zone be found structurally normal, as the classicists aver frequently to be the case. Also the clearly cut cases cited by the older writer are not explained away even after the expenditure of much industry and ingenuity.

The conviction grows, therefore, that there is truth in both dogmata, but that adequate explanations of many anomalous cases cannot be given without the injection into the argument of some new factor not as yet brought under scrutiny.

In the most tentative fashion I want to suggest here that the simple statement that a given patient is right-handed or left-handed is not adequate in the light of some cases to be mentioned later. No more information than is contained in this somewhat bald announcement is made by any of the writers on this topic, saving Byrom Bramwell,[5] yet it would appear that not only by investigating the question of a patient's handedness but also that of the prevailing type of handedness in his stock, will we be able to throw some light on a very obscure chapter of neurological medicine.

Case I.—My first case is that of massive injury (bomb wound) of the right temporosphenoidal and occipital lobes in a left-handed man without left-handed relatives or ancestry. No aphasia.

This patient was wounded on August 15, 1915, near Arras, and admitted to the Hôpital Militaire, Ris Orangis, on September 25. He stated that when making hand grenades he suddenly became unconscious, but he remembered dimly being bandaged in the trench and being carried to the second line. He rapidly recovered complete consciousness and never lost it again. On August 7 he was operated upon at Houdain. No convulsion nor headache. Never any difficulty with speech. His left arm and leg felt as though they had been slept on (comme s'il avait dormi dessus). This improved, but was present on admission to the Ris Hospital. He never had had pain in the affected limbs. On September 5 he said he felt very well. There was an infected wound in the right temporal and lower temporoparietal region. Its upper portion was clean, with a

[5] Lancet, 1899, p. 1473.

granulating surface measuring 8 by 2½ cm. In the posterior margin of the wound, behind the ear, there was a sinus about 5 cm. long, which extended inward and forward parallel to the external auditory canal. There was a marked bone defect, and the brain pulsated in the granulating area.

Examination showed pupils equal with brisk reactions; sight emmetropic on left side. The right eye was myopic by four diopters. Left homonymous hemianopia complete to fixation point.

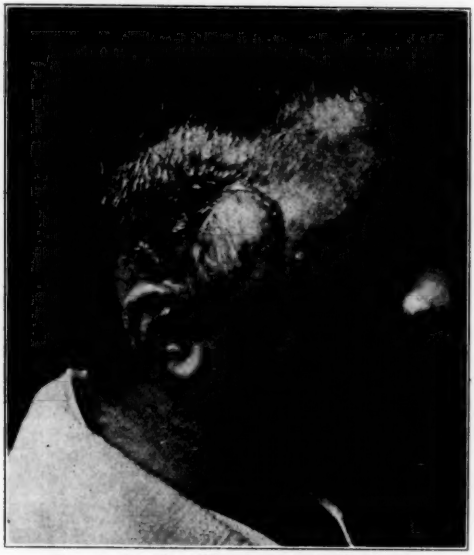

FIG. 1 (Case I).—Showing extent of wound.

Optic discs: The left showed venous tortuosity. The physiological pit was filled in and the left upper temporal quadrant was obscured by slight swelling. The right fundus showed no papilledema.

One may point out here that the formation of the myopic eyeball is such as to permit rapid drainage of fluid accumulated at the nerve head; as a consequence of this, papilledema is not a usual occurrence in myopic eyes. The presence of unilateral myopia in this patient probably accounts for the unilateral fundus changes. There was no nystagmus, diplopia, or strabismus. The lower jaw, on opening the mouth, swung to the right side, this being due not to a lesion of the motor root of the fifth nerve, but to fracture of the zygoma.

The general hypesthesia of the left side was seen in the face as elsewhere, but there was no localized fifth-nerve palsy. The left

lower face was distinctly paresed for both voluntary and emotional movement, thus showing damage respectively to the right facial cortical and the right optic thalamus.

The right membrana tympani had been ruptured and hearing proportionally diminished in the right ear. The tongue swung markedly to the right on protrusion. The swinging of the lower jaw to the right had overcome the tongue's hemiparetic tendency to go to the left. Palatal movements were quite normal.

Motor system: there was distinct and general softening and shrinking of the muscles of the left arm and leg, there being a differ-

FIG. 2 (Case I).—Showing large bone defect and wide distribution of fragments of grenade and bone in the temporo-occipital area.

ence between the left and right upper arm of 2.5 cm.; between the legs of 2 cm. No tremor or athetosis. Slight ataxia of the sensory type existed in the left upper extremity. The weakness in the left arm was more marked than in the left leg, though proportionately less marked than that in the left face. He could not stand on the left leg alone.

There was considerable titubation, probably the result of a lesion of Turck's bundle, uniting the temporal region to the pons. A distinct lowering of touch and superficial pain and deep muscle pain sensation existed over the whole of the left side of the body.

No mistakes were made in sense of position nor in the discrimination of temperature. Some slowness in the recognition of unseen objects held in the left hand, but in this regard also no mistakes were made.

Reflexes: All deep reflexes on the left side were exaggerated in degree. Abdominal reflexes were present on the right and absent on the left side. Plantar reflexes: right flexor, left extensor.

This patient was an intensely left-handed man, using that hand habitually for all complex acts. He had no motor speech difficulty whatsoever; no word deafness; he named promptly and accurately objects of which he had visual recognition. He had no apraxia or alexia. His memory was good. He read and wrote in a manner only interfered with by the complete hemianopia, of which mention has already been made. His father and mother were both right-handed persons. He was an only child, and knew of no other left-handed persons in his connection.

The chief point of interest in this patient seems to lie in the fact that he was left-handed to an extraordinary degree; he reversed the usual position of the knife and fork, and, while he wrote with the right hand, he was equally able to do so with the left.

Under these circumstances it would have been justifiable to have looked for a correspondingly marked disturbance of speech manifested in him as a result of the massive injury sustained by the right temporosphenoidal lobe. This injury not only was inflicted directly on the latter, but the fragments of the grenade and of driven bone are seen roentgenographically to have been flung through the cortex and to have become embedded in the right occipital pole.

The symptomatology here manifested has been presented in some detail in order that there may be shown the extensiveness of the disorganization of widely separated areas in the right brain. We are, therefore, not straining our postulate if we suppose that in this case we have to deal not only with an injury to the right transverse gyri of Heschl, but also with one affecting the commissural fibers between them and the homolateral half center of vision.

In the descriptions of the type of speech defect consequent upon temporal lesions there has been much fluctuation of opinion. Even the most recent text-books reproduce the idea that word-deafness is characteristic of lesions in the speech area of these regions, ignoring the evidence which goes to show that only the most sudden catastrophe successfully destroying at a blow the transverse gyri will produce such an aphasic extremity. The intermediate defects produced by disease processes are manifested, not by a cleanly cut inability to comprehend heard words, but by a depression of power to recall words voluntarily, especially the names of persons, places, and things.

To this phenomenon is usually added that of failure to name an object of which there is visual recognition. These two defects are, at first sight, almost of identical nature and origin, but it may be

pointed out that the former depends on a depression of function in the cortical area containing the memories of words, while the latter arises from an interruption of the subcortical fibers uniting the visual and auditory centers.

In this patient, then, we have, to a maximum degree, an injury which, according to the teachings both of the classicists and their assailants, by its rapidity and extent, should have produced a maximum disorder of speech. There was no disorder.

In the literature of aphasia one finds that but few cases disagree with the general hypothesis that in right-handed persons the centers of language are situated on the left side of the brain. In a few instances in which aphasia has resulted from injury to the right brain some anomalous and adventitious circumstance has usually been brought forward to account for the situation. For example, it was found by Oppenheim[6] in two cases of affection of the right temporal convolution that in one there was acquired left-handedness in a woman, aged fifty-nine years, who had been found to use her left hand for all purposes owing to injury at the age of seventeen years; in the other case there were two tubercles in the right temporosphenoidal lobe, and aphasia is reported only to have appeared when the patient was already moribund, and, according to Oppenheim's assumption, as a result of toxic action on the auditory center in the left side of the brain.

Again, Long,[7] after describing a case of embolic right-sided hemiplegia with sensory aphasia in a left-handed woman in whose brain was found a wide-spread destruction of Broca's area and annectant gyri, accounts for the absence of motor aphasia symptoms by the hypothesis of an immediate assumption of speech function on the part of the uninjured hemisphere, as casuistic a theory as can easily be found even in the literature of this somewhat nebulous topic.

No such peculiar or recondite data are obtainable in this case to account for the escape of speech faculties supposedly resident in a portion of highly damaged brain tissue. In view of the seriousness of the lesion it is only possible for us to suppose that the patient's immunity from this disaster lies in the fact that, despite his left-handedness, he is also left-brained. An adumbration of why this may be so is the *raison d'etre* of this discussion.

The second case to which I wish here especially to refer is one published by Byrom Bramwell.[8]

CASE II.—A man, aged thirty-six years, suffered from embolic right-sided hemiplegia and aphasia. He was left-handed and had been so all his life. He did everything but write with his left hand. None of his near relatives or ancestors were known to be left-handed. He was a twin; his twin brother was right-handed. The explanation

[6] Quoted by Bruns in Geschwülste des Nerven systems.
[7] L'Encéphale, 1913, viii, 520.
[8] Loc. cit.

given by Bramwell of this individual's peculiar reaction to his vascular accident is that, in spite of his left handedness, the left brain was educated as a speech area by reason of his having been taught to write with his right hand. However, I would point out that perhaps not sufficient weight is given to his isolation as a left-handed person in a stock entirely right-handed; and also that Bramwell's theory does not explain such cases as that reported by Senator:[9] an embolic left hemiplegia with aphasia in a right-handed individual. It is most unfortunate that it was impossible for Senator in the case of this woman to discover whether or not her stock contained a left-handed strain.

The third case was seen by me in the New York Hospital—a completely left-handed man in the service of Dr. Charles Gibson, with whom I saw him in consultation. He had sustained a fracture in the right occipitotemporal region with right middle meningeal hemorrhage.

Craniectomy had been performed, a bone defect of two by four inches having been made over the affected areas.

Following the injury the patient had suffered a left hemiplegia, from which he had recovered at the time of my examination. At intervals, however, he suffered from severe left-sided convulsions.

Despite his left-handedness, which was complete except for writing, associated with a severe injury to the right brain, he never had had the slightest interference with the function of speech.

This patient's relatives were all right-handed. He had lived, as had the French soldier whose condition was first described, as a member of a village community, in which, in both instances, were included many of their relations. Each man was quite positive that he was the only left-handed member of his stock.

We have now considered three cases of left-handed persons in whom brain injury produced phenomena opposed in their combinations to what we should expect in the light of our usual teachings. It is proper, then, to consider a like number of right-handed individuals showing similar peculiar results from similar cerebral catastrophes.

One may point out that, in the first set, our evidence as to each patient's variation from his stock-handedness must be of a negative character; but in the three cases now to be described, each right-handed individual can designate specifically relatives individually peculiar in that they differ from ordinary mankind in using their left hands for all complicated activities.

The first of this second series (Case 4) is that of a right-handed girl, aged twenty-two years, of whom I had charge in the service of Dr. James Taylor at the National Hospital in London. This patient repeatedly had severe attacks of Jacksonian convulsions confined

[9] Charité annalen, 1904, xxviii, 150.

to the left side of the body. These fits, occurring under observation over a period of twelve months, were always followed by a severe transient left hemiplegia and equally severe transient aphasia. The patient, herself right-handed, had a left-handed father and a left-handed mother, both of whom presented themselves for observation.

For the reports of the next two cases I am indebted to Dr. Charles Elsberg and Dr. E. D. Fisher respectively.

The history given by the former (Case 5) is that of a young man suffering from a right-sided deeply subcortical Rolandic glioma, on whom was performed at the New York Neurological Institute a right subtemporal decompression. He had complete aphasia for ten days following the operation. He was himself right-handed, but had two brothers both of whom were left-handed.

Patient.	Individual handedness.	Stock handedness.	lesion.	Physical results of lesion.	Speech.
Male, aged 25 years	Left-handed	Right-handed	Grenade wound right temporo-sphenoidal and occipital lobes	Left hemiplegia Left hemihypesthesia Left homonymous hemianopia	No disturbance.
Male, aged 36 years	Left-handed	Right-handed	Left brain embolus	Righ hemiplegia	Aphasia.
Male, aged 23 years	Left-handed	Right-handed	Right middle meningeal hemorrhage; skull fracture	Left hemiplegia Left-sided focal epilepsy	No disturbance.
Female, aged 22 years	Right-handed	Parents both left-handed	Right Rolandic tumor (gumma)	Left-sided focal epilepsy; transient attacks of left hemiplegia	Complete aphasia after each fit.
Male, aged 28 years	Right-handed	2 brothers, left-handed	Right subcortical Rolandic glioma; right subtemporal decompression	Slight left hemiplegia	Aphasia.
Female, aged 67 years	Right-handed	Mother, brother, daughter all left-handed	Right brain hemorrhage	Left hemiplegia	Aphasia.

The last case (Case 6) is that of a woman, aged sixty-seven years, under the care of Dr. Fisher. She had sustained a cerebral hemorrhage, as a result of which she had a left hemiplegia and a considerable degree of sensorimotor aphasia. She was right-handed, but her mother had been left-handed. She had a left-handed brother and a left-handed daughter.

The reasons why 95 per cent. of the human race are right-handed have been debated without definite conclusion for the past thirty years. An enormous number of theories have been elaborated, and to almost all of them many objections can be raised.

Barnes[10] is content to say that right-handedness is essentially hereditary, while Gowers[11] quotes the amazing notion that insofar

[10] Lancet, 1903, i, 331.

[11] Lancet, 1902, ii, 1719.

as the human family took origin north of the equator, our first ancestors, seeing the sun travel from left to right, through manual demonstration of the fact and graphical reproduction of it, would naturally lay down in themselves the primitive elements of dexterity. Almost as difficult of proof are the hypotheses which endeavor to explain our asymmetry through the different widths of the carotids, the different blood-pressures in these vessels, and their differences in anatomical origin.

Schaeffer[12] reports five right-handed cases, all with visceral transposition, as evidence against the theory that the right-sided position of the liver should inevitably make us more ready to employ the homolateral arm and hand.

Also Bastian's statement[13] that the specific gravity of the left brain is greater than that of the right, has not met with corroboration and if it had been confirmed, would not materially assist in laying bare the underlying factors of the condition.

Dareste[14] has advanced an interesting hypothesis to the effect that the embryo, applied first to the vitellus by its anterior surface, invariably turns on itself and becomes applied, in the majority of cases, by its left side. He asserts, with little enough proof however, that in this way development of the left side is impeded.

An almost identical theory is put forward by Brandt,[15] and a parallel idea from a strange source, that of the aborigines of North Queensland, is to the effect that right and left-handedness depends entirely on the side of the mother to which the infant presents at the moment of birth.[16]

It is apparently certain that all animals, notably the anthropoid apes, are either handed, and from protopaleolithic implements found in France and Kent it would seem that among our primeval forebears the domination of the left hand was as usual as that of the right.[17] The directions of the flakings on primitive meat and corn crushers of the neolithic period would seem to point to the same conclusions. A gradual recognition in the minds of the earliest men of the necessity of shielding the heart may have led to a tendency to right-handedness which has been transmitted to the bulk of the human family.

Stier[18] in 5000 soldiers found only 4.6 per cent. left-handed, but in over 60 per cent. of these there was obtained a very definite history of a sinistral tendency in the stock of each individual examined.

The percentage of cases in which this left-handed trend is present

[12] Berlin. klin. Wchnschr., 1911, No. 7, p. 295.
[13] Jour. Ment. Sci., 1866, p. 28.
[14] Bull. de la Soc. d'anthropologie, 1885, 415.
[15] Biolog. Centralblatt, 1913, xxxiii, 361.
[16] Chamberlain, Science, 1903, xviii, 788.
[17] Astley, Lancet, 1901, i, 1246.
[18] Monograph, Jena, 1911.

in the forebears must be—and this also is affirmed by Stier—very much larger than can be easily proved by direct statistics.

It would appear, then, that from the cases reported that this trend when present in the stock may produce in the few right-handed individuals of the sinistral stock a condition of brain similar to their collateral relatives and ancestors, with the result that the speech area in such persons becomes developed in an ectopic position. Likewise a left-handed person occurring eccentrically in a right-handed stock is dominated by the trend of that stock rather than by his own individual peculiarities.[19]

These matters would seem to be of small enough practical importance, but one may suggest that the considerations in favor of and against cranial operative procedures are not infrequently influenced by the fear of destruction of the areas governing the function of speech. On this account, apart from the academic interest of the question, it behooves us to record any facts seeming to assist us to increased accuracy of endeavor.

CIRCUMSCRIBED CYSTS OF THE LEPTOMENINGES, WITH THE REPORT OF A SUCCESSFUL OPERATIVE CASE.

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Circumscribed cystic spinal meningitis is not an uncommon cause of spinal cord compression, and since operative interference offers prompt relief from an otherwise progressive and irreparable injury, its early recognition is of great importance. Among 45 cases operated upon for suspected tumor of the cord by Krause,[1] cystic meningitis or, as he terms it, arachnitis adhesiva circumscripta was found in 11, or about 24 per cent. Despite the fact, however, that cystic spinal meningitis can no longer be regarded as a rarity, the literature upon the subject is still very scanty and a general knowledge of the condition is lacking.

Spiller[2] wrote in 1908: "A collection of the clear fluid in a cyst

[19] July 26, 1916. Man, aged thirty-one years. Seen in Bellevue Hospital. Almost complete palsy of left face and left arm, much weakness in left leg; left homonymous hemianopia; left hemianesthesia. Probable luetic cerebral thrombosis. Left-handed from infancy; prefers to write with the left hand. Never any speech difficulty even immediately following onset. Patient is the only left-handed individual in a family of seven, and in a large connection the members of which are well known to him.

[1] Surgery of the Brain, iii, 1055 (Rebman, New York).

[2] Am. Jour. Med. Sc., 1909, cxxxvii, 95.

of the spinal pia-arachnoid is a condition little known in America, as only one case occurring in this country is on record (Spiller, Musser, and Martin), and only a few are found in German literature. So far the French and English journals contain no examples." Since this was written several excellent papers have appeared. The first satisfactorily reported case was that of Spiller, Musser, and Martin,[3] in 1903. Since then instances of the affection have been reported by Krause,[4] Oppenheim,[5] Bruns,[6] de Montet,[7] Mendel and Adler,[8] Horsley,[9] Bliss,[10] Weisenburg and Müller,[11] Munro,[12] and Mills.[13] Krause, in his *Surgery of the Brain and Cord* (translation, Rebman, New York), gives very clear illustrations of the condition. That the disease is by no means so rare as the literature would indicate is attested by the experience of Munro,[14] who after reading the description of a case was able to report five instances from his own previous experience in which no satisfactory diagnosis had been registered at the time of operation. One unfamiliar with the condition might easily fail to recognize it at operation.

Skoog[15] has recently reported two instances of leptomeningeal cysts, and reviews the literature. He makes the absolutely incorrect assertion that only four instances of simple uncomplicated cysts of the pia-arachnoid have been recorded, basing his statement upon what he terms a "thorough search of the literature." And yet the author fails even to mention the perfectly typical case that Weisenburg so fully recorded in this JOURNAL in 1910. Skoog apparently has undisclosed criteria of his own as to just what constitutes a leptomeningeal cyst, for he discredits Munro's five cases with the simple remark that "it is necessary to reject his reported cases." The unbiased reader of Munro's article will not, I think, feel the same necessity that Skoog so cryptically confesses.

Before proceeding to a discussion of circumscribed cystic spinal meningitis a very typical instance of the affection which recently came under our observation will be briefly reported:

CASE HISTORY.—*Progressive paralysis of both legs for one year; no pain; paresthesia of legs; anesthesia below mid-abdomen; bladder disturbances; operation and evacuation of localized leptomeiningeal cyst; marked improvement.*

[3] Univ. of Penn. Med. Bull., 1903, xvi, 27.
[4] Verhandl. d. Deutsch. Gesellsch. f. Chir., 1907, xxxvi, 598.
[5] Beitrage zur Diagnostik und Therapie der Geschwulste im Bereich des Centralen Nervensystems, Berlin, 1907.
[6] Berl. klin. Wchnschr., 1908, p. 1753.
[7] Cor.-Bl. f., schweiz. Aerzte, 1908, p. 698.
[8] Berl. klin. Wchnschr., 1908, xlv, 1596.
[9] Brit. Med. Jour., 1909, i, 513.
[10] Jour. Am. Med. Assn., 1909, liii, 885.
[11] AM. JOUR. MED. SC., 1910., cxl, 719, No. 5.
[12] Surg., Gynec. and Obst., 1910, x, 235.
[13] Jour. Nerv. and Ment. Dis., 1910, xxxvii, 529
[14] Loc. cit.
[15] Jour. Am. Med. Assn., 1915, lxv, 394.

The patient, J. K., a colored man, aged twenty-six years, was brought to the Virginia Hospital because of complete paralysis of both legs.

The family and past histories were devoid of importance. He denied gonorrheal or syphilitic infection, and up until the present trouble had been healthy. No symptoms of tuberculosis.

About fifteen months ago the right leg began to grow weak and felt a little stiff. This was followed in a few weeks by similar symptoms in the left leg. His gait became unsteady and he staggered "like a drunken man." Three months after onset his legs had become so weak that he was forced to remain in bed most of the time. Except when assisted into a chair he has been in bed for the past twelve months.

The patient is positive that he has never suffered any pain during his present illness. No history of anything resembling root-pain can be elicited even with strong suggestion. He has had numbness of both legs from time to time, and is aware that the sense of touch is at present diminished in the legs.

During the past year he has had periods of frequency and urgency of urination, but has never been incontinent. At present he says he notices no abnormality of the bladder or rectal functions.

Physical Examination. The patient is a thin, poorly nourished man, lying in the dorsal decubitus, with both legs strongly flexed on the thighs. The head, neck, chest, and abdomen present no features of importance. No general or local adenopathy.

Neurological Examination. The pupils are equal in size, regular in outline, and both react actively to light and during accommodation. No nystagmus, strabismus, or diplopia. Vision good. Fundi negative. Hearing is acute and equal in the two ears. The other cranial nerves are likewise normal.

As the patient lies in bed the legs are constantly flexed, and upon the slightest stimulation they pass into a state of tonic spasm. All the muscles of the legs are involved in this spasm, and the abdominal muscles are rigid and spastic. Both legs are almost completely paralyzed; he can move them slightly after great effort, but cannot in any way control them. Upon attempting passively to flex and extend the patient's legs a condition of great spasticity is encountered which prevents any but the very slowest manipulations. The legs cannot be completely extended.

Sensation to touch, pain, heat, and cold is deficient over the legs and trunk up to the level of the ninth dorsal skin segment. The upper thighs and trunk are not completely anesthetic, but the patient is able to indicate with constancy and accuracy the line below which sensation is impaired. On the legs and feet, sensation is practically abolished. The tests for muscle and joint sense are untrustworthy because of the great degree of spasticity, but from passive movement of the toes it seems impaired.

The reflexes are normal in the upper limbs, but all deep reflexes are exaggerated in the legs. There is double ankle clonus, and the Babinski reflex is bilaterally positive. Because of the board-like spasticity of the abdominal muscles the superficial abdominal reflexes cannot be satisfactorily tested.

There is no sphincter disturbances at present. The patient is completely bed-ridden. The temperature and pulse are normal.

A spinal puncture was performed and 8 c.c. of fluid under apparently diminished pressure was obtained. The fluid had a distinct yellowish tinge, though not frankly yellow in color. The cell count showed the presence of three lymphocytes to the cubic millimeter. The Noguchi globulin reaction indicated the presence of a very marked excess of protein material. With the heat and acetic acid test a heavy, floccular precipitate formed in the fluid. The significance of this picture—xanthochromia, protein excess with low cell count—has been discussed recently by one of us in this JOURNAL (Hanes, 1916, clii, 66). Suffice it to say that its presence strengthened the probable diagnosis of spinal cord tumor. The Wassermann reaction was negative in both blood and spinal fluid.

The clinical diagnosis of extramedullary tumor compressing the spinal cord was registered, and under ether anesthesia laminectomy was performed. The dura was exposed at the level of the fifth, sixth, and seventh dorsal vertebræ. It did not pulsate. Upon opening the dura at the level of the sixth dorsal vertebræ a cherry-sized translucent, delicate-walled cyst presented at once in the dorsal incision. This was incised with the escape of perfectly clear, colorless fluid, and the cyst structure collapsed. There was apparently only one cyst. The spinal canal was explored thoroughly above and below, but no other tumor mass could be found. The cord seemed flattened and somewhat compressed by the cyst, and the vessels below the level of the cyst were distinctly engorged and tortuous.

The dura was sutured and the wound closed. Healing was rapid, and on the eighth day after the operation was complete.

The improvement in the condition of the patient was immediate and quite remarkable. On the day following the operation he could move the legs with considerable certainty, and this improvement continued until on the tenth day following the operation he was able to stand for a moment or two alone. Since this time there has been a gradual gain in the strength and control of the legs, but improvement has been slower than perhaps would have been the case had the patient's circumstances permitted efficient physical therapy. The muscles of both legs are still spastic, though much less so than before operation, and the Babinski reflex is still bilaterally positive.

Six weeks after the operation lumbar puncture was again performed. The fluid was now quite normal in appearance, without

a trace of color. There were four cells to the cubic millimeter, with only a faint trace of proteid, as contrasted with the former great excess. This finding proves incontestably that the xanthochromia and protein excess present in the spinal fluid before operation were caused by the cystic tumor which had formed a cul-de-sac below its site of growth. Upon restoring the integrity of the canal the fluid promptly resumed its normal character.

The exact etiology of circumscribed cystic formations in the spinal leptomeninges is uncertain. The pia-arachnoid spaces of the brain and cord form a true serous cavity analogous to the pleural and peritoneal spaces, and it is reasonable to assume, in view of the frequency of inflammatory adhesions in other serous cavities, that the delicate leptomeninges, as the result of either septic or aseptic inflammatory processes, form adhesions which may produce single or multiple cysts. The histological structure of the trabeculated pia-arachnoid membrane would seem to favor such a process. The occurrence of aseptic meningeal inflammations of various degrees, from meningismus to true purulent meningitis, with thousands of leukocytes in the spinal fluid (Zabel[16]), is not sufficiently recognized. Such aseptic inflammatory processes might easily lead to leptomeningeal adhesions and cyst formations.

Trauma has closely preceded the development of certain cases of cystic meningitis, and several writers mention it as an etiological factor.[17] [18] [19] We are inclined to believe that traumata by the production of small hemorrhagic effusions into the leptomeninges may cause toxic inflammation, with consequent adhesions. That inflammatory processes in structures in the neighborhood of the pia-arachnoid, such as spinal tuberculosis or osteomyelitis, may ultimately lead to localized leptomeningitis is well recognized. In general it seems fair to say that any process, either septic or aseptic, which causes localized meningeal inflammation, may through the formation of adhesions, produces cysts of the pia-arachnoid.

The pathological condition, as seen at operation, consists in the presence of one or more cysts, with very delicate walls. When the dura is incised the thin-walled, translucent, cystic structure protrudes under the pressure of the contained fluid. Upon puncturing the cyst the walls collapse and become inconspicuous. If in opening the dura one should puncture the pia-arachnoid cyst it is easily understandable that the condition might pass unrecognized. Certainly from some of the descriptions published, where "upon opening the dura a large quantity of fluid escaped under pressure," one is forced to conclude that a cyst was opened along with the dura.

[16] Mitt. a. d. Grenzge. d. Med. u. Chir., 1913, xxv, 211.
[17] Mendel and Adler, loc. cit.
[18] Horsley, Victor, loc. cit.
[19] Bliss, M. A., loc. cit.

The cord shows the effect of the pressure which the cystic tumor has exerted, being somewhat flattened and compressed, with engorgement of the pial vessels. In our case the veins of the cord distal to the site of the cystic obstruction were markedly congested and tortuous, and we are convinced that this obstruction to the venous flow of blood accounts for the curious condition of the spinal fluid found in this case. The fluid was yellowish, with only 3 cells to the cubic millimeter; but it contained an enormous excess of protein, and coagulated on standing. In short, the fluid obtained by lumbar puncture had the characteristics of a transudate such as is commonly encountered as the result of venous obstruction. Spinal fluids with the characteristics just described are not at all uncommon, and are of very great practical significance, for they always indicate compression of the cord with the formation of a lumbar cul-de-sac.

The symptoms of circumscribed serous meningitis are those of cord tumor. We doubt the possibility of making a differential diagnosis between extramedullary tumor of the cord and cyst of the pia-arachnoid. Cysts, indeed, when circumscribed are tumors capable of exerting pressure which causes almost complete transverse blocking of the cord functions. We have never seen more intense spasticity or more complete paralysis than was present, for example, in our case, even in long-standing cases of extramedullary neoplasm.

Horsley[20] enumerates some eight differential points which he thinks are of service in the diagnosis of circumscribed serous meningitis. Horsley, however, has included in his paper certain cases which cannot properly be regarded as instances of circumscribed cystic meningitis, but are rather examples of meningomyelitis. Aside from this, moreover, one of us while working at the National Hospital for Paralyzed and Epileptics in London had the opportunity of studying carefully a case of circumscribed cystic meningitis which violated practically all of Horsley's differential points. Horsley operated for cord tumor and found a circumscribed cyst. Oppenheim[21] thinks cysts of the pia-arachnoid cannot be differentiated from extramedullary neoplasms. Fortunately, the need of separating the two conditions does not exist, for both demand precisely the same operative treatment. It is far more important to recognize that both neoplasms and cysts may present most atypical pictures and not to be misled thereby.

The symptoms and signs as reported by various observers consist of pain, disturbances of sensation, paralysis or paresis, abnormality of the reflexes, and sphincter disturbances. These are manifestations of transverse lesions of the cord from whatsoever cause, and in diagnosis one must eliminate syphilitic and tuberculous disease,

[20] Loc. cit.

[21] Lehrbuch der Nervenkrankheiten, 1913, i, 388 (full literature).

acute meningomyelitis, extramedullary tumors as well as traumatic injuries, such as fracture dislocation of the vertebræ. In the process of differential diagnosis a thorough examination of the spinal fluid is of the greatest value. It is impossible to agree at all with Munro[22] when he states that "nearly every writer condemns lumbar puncture . . . as an aid to diagnosis except negatively." As we have shown in our case the condition of the spinal fluid was of the greatest positive support in the diagnosis of cord compression as opposed to meningomyelitis, gumma, or parenchymatous cord lesions.

Pain has been a prominent feature of most of the cases recorded. Our patient denied absolutely having suffered any pain at all. Pain was formerly regarded as an essential clinical feature of spinal cord neoplasms, but we now know that extramedullary tumors may exist with none or only insignificant pain. The same is doubtless true of cystic meningitis.

The treatment of leptomeningeal cysts is wholly surgical. The time is rapidly approaching when *exploratory laminectomy* will be resorted to with greater frequency than is done at present. The operation is a simple one, easily within the powers of any competent surgeon. The removal of the spinous processes and dorsal laminæ does not materially weaken the spinal column, and the operative wound heals promptly. It is, of course, unnecessary to emphasize that laminectomy should never be performed except with the support of a competent neurological opinion.

THE TREATMENT OF FRACTURE OF THE SPINE.

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There has been such an advance in surgical methods the past decade that conditions which formerly did not warrant surgical interference are now being successfully treated.

The recent developments in cranial and in intestinal surgery are illustrative of the advances made in surgery in general. This is specially true of the progress made in spinal-cord surgery during the last five years. However, as in any new field, progress is hampered by the beliefs and practises of the past, and that has operated strongly against progress in the rational treatment of spinal fractures.

Fracture of the spinal column with damage to the cord or roots is considered, and rightly so, a most serious injury. Though the

[22] Loc. cit.

spinal cord is the best protected structure of the body, once the bony canal is shattered the cord is most susceptible to hurt, and its extremely low, or perhaps absent, regenerative powers makes it unique among the body structures. The integrity of the protecting bony canal once broken it becomes a menace by reason of fragments driven into the cord and by its inelasticity prevents the escape of inflammatory exudates, with resulting compression of the nerve fibers.

It is the advice and practise of a majority of surgeons that in fracture of the spine, with damage to the cord, without obvious deformity and determinable loose fragments of bone, the symptoms are due to contusion or laceration of the cord or hemorrhage, and that it is better to defer operation until the symptoms have come to a standstill; and that fracture with immediate and complete abolition of function below the lesion indicates division of the cord, and no operation is justifiable. This attitude is, I believe, most questionable, and cannot be defended on theoretical, experimental, or clinical grounds.

In the discussions that have gone on in late years as to the advisability of early operation in these injuries, the opponents of early operation have maintained that laceration of the cord cannot be remedied by operation, and that the nerve fibers, if severely injured, degenerate whether compression is immediately removed or not. That removal of pressure by early operation will not cause the already destroyed fibers to regenerate is true. But the opponents of early operative interference have apparently overlooked several important facts. That is, in fractures with damage to the cord, short of a complete transverse lesion, there are many fibers and tracts that escape injury wholly or in part. And there are other factors that will work harm to the nerve fibers in addition to the damage received at the moment of injury. If operation is not done, compression by bone, by hemorrhage, or the quickly following edema will destroy the already damaged fibers and involve many of the sound ones. Interruption of conductivity of nerve fibers after fracture does not necessarily mean that those fibers are destroyed. In practically every case of damage to the cord, short of complete lesion, many of the interrupted fibers will later functionate, and it is to preserve the integrity of the sound fibers and to give the best chance of recovery to the damaged but not destroyed fibers that early operation is urged. In former years laminectomy was a formidable procedure, and operation was delayed on this account. But at the present time the dangers of laminectomy in skilled hands is but slight in comparison to the possible benefits.

Fracture of the spine may be due to direct force, and in this case the fracture may occur in any part of the spinal column. But the more usual cause is indirect force, such as severe falls on head, shoulders, or buttocks, or, more commonly, violent flexion, extension, or torsion of the spine by extreme pressure. In these

cases the fracture is usually located in the lower cervical region or in the neighborhood of the dorsolumbar junction. Dislocation may accompany the fracture and the displaced vertebra may remain in the abnormal position or spring back into its normal place. It is in fracture-dislocation that the most serious damage to the cord is done.

According to Pearce Bailey, in almost one-third of the cases of fracture of the spine the cord escapes injury. These cases are to be treated, as are skeletal breaks elsewhere, by immobilization, and are not of special interest to the neurological surgeon unless symptoms of cord or root involvement arise later, due to new-bone formation. Case I is a good example of this type of spinal fracture.

Symptoms of cord injury in fracture are due to the following factors:

1. To fragments of displaced bone causing contusion or laceration of the nerve fibers, or a narrowing of the canal by the fractured laminæ or a projection backward of a vertebral body, causing compression of the cord. In these cases the symptoms of cord injury arise immediately after the accident.

2. Hemorrhage either into the cord substance (hematomyelia), causing laceration of the fibers, or hemorrhage around the cord, either intra- or extradural, causing compression of the cord. In these cases the symptoms come on shortly, may be hours after the injury, and are usually progressive.

3. Edema both within and around the cord, causing compression of the fibers. In itself edema gives rise to symptoms that appear, like those due to hemorrhage, some hours after the accident, and these symptoms are progressive. This edema, present after every injury to the cord, and by its compressive effects so destructive to the nerve fibers, forms one of the chief reasons for early operation. Its power to harm has been overlooked in the past, and recent operations have shown that in many cases symptoms indicating injury or compression of bone are really due to the compressive and destructive effects of the edema.

4. Narrowing of the spinal canal at the site of injury by new-bone growth or the formation of scar tissue. Here the symptoms arise months after the injury.

These factors operate singly or in combination. It is only in rare cases and in the slighter injuries that these factors operate singly. In the majority of fractures of the spine, two or more, and at times all, of these factors are seen. That is, in fractures with laceration or compression of the cord by displaced bone there is usually hemorrhage in or around the cord, it is always followed by edema, and often later by narrowing of the cord space by new-bone growth or scar formation. However, in nearly every case one factor, such as compression by bone or hemorrhage in or about the cord, so predominates as to render the other factors

negligible for the time being, though later these other factors will add their quota to the sum total of the symptoms and have a strong effect on the probable results. It must not be forgotten in making a diagnosis and determining the probable factor or factors in the causation of the symptoms that, as mentioned above, immediate interruption of conductivity, whether partial or complete, does not necessarily mean laceration of the fibers or tracts interrupted. In addition to the loss of function of the damaged fibers the shock or jar of the injury may cause an inhibition of function of the sound fibers, more or less complete for a variable period of time, with later an almost complete functional recovery of these fibers. So that a case in which the symptoms coming on at once may seem to be due to laceration of the cord by displaced bone may be really one of compression by hemorrhage or edema, the primary symptoms being due to a functional inhibition of the above type. If these symptoms occurred in a structure of greater reparative power than the cord, a delay in operation would be justifiable, in order to permit of recovery of the fibers from the initial injury; but delay, with tissue so feebly resistant as the cord in the presence of continued compression by bone, hemorrhage, or edema may work permanent damage.

Fracture with Symptoms of Partial Abolition of Function. In cases of this type there is partial and irregularly distributed motor paralysis with abolition of some of the reflexes and areas of anesthesia below the site of the injury and probable disturbances of sphincteric control. In these cases the symptoms are due either to contusion, laceration, or compression of the cord by the crushed vertebræ or to compression by hemorrhage in or around the cord.

Experimental studies of contusion of the cord show, in proportion to the severity of the contusion, disintegration of the axis-cylinder; but this is usually less marked than in cases of compression. In continued compression, in which the hemorrhage becomes an added element, the nerve fibers disintegrate and finally liquefy.

In partial lesions of the cord there are found destroyed, damaged, and sound fibers side by side. Of the destroyed fibers nothing is to be expected; they will not regenerate. The fate of the damaged and of many of the sound fibers depends on whether the factors producing the injury are temporary or permanent. These factors are compression by bone, blood, and the certain edema which appears after every injury to the cord. If this compression is quickly removed not only will the sound fibers be preserved, but functional and even anatomical repair will take place in many of the damaged but not destroyed fibers. But if compression due to any or all of the above-mentioned three factors is at all severe, and is allowed to continue for as short a period as four days, not only will secondary degeneration appear in the damaged fibers, but many of the sound fibers will also be involved.

The late John B. Murphy said: "In fractures without considerable displacement we are justified in assuming that the cord is not suffering continued compression regardless of the degree of paralysis; operation is not indicated. If this paralysis is due to laceration it will not be improved by operation. If it is due to contusion it will recover without operation."

This advice might be good if displaced bone was the only factor in compression. But it overlooks the factors of hemorrhage and edema which, unless removed by operation, augment and continue the initial compression. It is true that lacerated fibers will not be improved by operation. It is not for their sake early operation is urged, but to give the best chance of recovery to the adjacent damaged compressed fibers and to preserve the sound fibers.

In contusion, also, hemorrhage and edema, at least edema, are always present, and if not relieved early by operation, will increase the ultimate impairment.

Allen has demonstrated the baneful effects of this edema by the improvement following experimental incisions into the cord after spinal fracture in animals.

This condition of cord edema is analogous to that seen in the cranial cavity after fractures of the skull. And just as the urgency of the symptoms in fracture of the skull call not so much for the location of the fracture and determination of hemorrhage, but for the relief of the general intracranial pressure, so in spinal fractures the demand is for relief of intraspinal pressure; and this is even more important than in head injuries, for the so-called silent areas of the brain do not exist in the cord where serious damage to any part of the cord means permanent loss of function. The necessity of accurate diagnosis as to whether the damage is caused by contusion, laceration, or compression by bone, hemorrhage, or edema does not exist. The urgent indications are for "spinal decompression" by laminectomy with free opening of the dura, giving the cord fibers the best possible opportunity for repair. (See Case III.)

One stated objection to the early operation, or in fact to any operation in the absence of deformity, is that in many reported cases of early laminectomy little or no improvement followed, though no displaced bone was found; "and as the cord appeared normal, the dura was not opened." Such observations are similar to those regarding so-called cranial decompressions when the dura is not opened.

Compression of cord fibers by edema will not be relieved by the removal of the laminæ alone. And just as in head injuries, removal of bone will not relieve the intracranial pressure unless the dura is also opened, so in spinal fractures a free opening of the dura is most important and should always be done.

J. T. Bottomley advises in partial lesions of the cord that "if fingers or the roentgen-rays find no deformity of bone, then it is

negligible for the time being, though later these other factors will add their quota to the sum total of the symptoms and have a strong effect on the probable results. It must not be forgotten in making a diagnosis and determining the probable factor or factors in the causation of the symptoms that, as mentioned above, immediate interruption of conductivity, whether partial or complete, does not necessarily mean laceration of the fibers or tracts interrupted. In addition to the loss of function of the damaged fibers the shock or jar of the injury may cause an inhibition of function of the sound fibers, more or less complete for a variable period of time, with later an almost complete functional recovery of these fibers. So that a case in which the symptoms coming on at once may seem to be due to laceration of the cord by displaced bone may be really one of compression by hemorrhage or edema, the primary symptoms being due to a functional inhibition of the above type. If these symptoms occurred in a structure of greater reparative power than the cord, a delay in operation would be justifiable, in order to permit of recovery of the fibers from the initial injury; but delay, with tissue so feebly resistant as the cord in the presence of continued compression by bone, hemorrhage, or edema may work permanent damage.

Fracture with Symptoms of Partial Abolition of Function. In cases of this type there is partial and irregularly distributed motor paralysis with abolition of some of the reflexes and areas of anesthesia below the site of the injury and probable disturbances of sphincteric control. In these cases the symptoms are due either to contusion, laceration, or compression of the cord by the crushed vertebræ or to compression by hemorrhage in or around the cord.

Experimental studies of contusion of the cord show, in proportion to the severity of the contusion, disintegration of the axis-cylinder; but this is usually less marked than in cases of compression. In continued compression, in which the hemorrhage becomes an added element, the nerve fibers disintegrate and finally liquefy.

In partial lesions of the cord there are found destroyed, damaged, and sound fibers side by side. Of the destroyed fibers nothing is to be expected; they will not regenerate. The fate of the damaged and of many of the sound fibers depends on whether the factors producing the injury are temporary or permanent. These factors are compression by bone, blood, and the certain edema which appears after every injury to the cord. If this compression is quickly removed not only will the sound fibers be preserved, but functional and even anatomical repair will take place in many of the damaged but not destroyed fibers. But if compression due to any or all of the above-mentioned three factors is at all severe, and is allowed to continue for as short a period as four days, not only will secondary degeneration appear in the damaged fibers, but many of the sound fibers will also be involved.

The late John B. Murphy said: "In fractures without considerable displacement we are justified in assuming that the cord is not suffering continued compression regardless of the degree of paralysis; operation is not indicated. If this paralysis is due to laceration it will not be improved by operation. If it is due to contusion it will recover without operation."

This advice might be good if displaced bone was the only factor in compression. But it overlooks the factors of hemorrhage and edema which, unless removed by operation, augment and continue the initial compression. It is true that lacerated fibers will not be improved by operation. It is not for their sake early operation is urged, but to give the best chance of recovery to the adjacent damaged compressed fibers and to preserve the sound fibers.

In contusion, also, hemorrhage and edema, at least edema, are always present, and if not relieved early by operation, will increase the ultimate impairment.

Allen has demonstrated the baneful effects of this edema by the improvement following experimental incisions into the cord after spinal fracture in animals.

This condition of cord edema is analogous to that seen in the cranial cavity after fractures of the skull. And just as the urgency of the symptoms in fracture of the skull call not so much for the location of the fracture and determination of hemorrhage, but for the relief of the general intracranial pressure, so in spinal fractures the demand is for relief of intraspinal pressure; and this is even more important than in head injuries, for the so-called silent areas of the brain do not exist in the cord where serious damage to any part of the cord means permanent loss of function. The necessity of accurate diagnosis as to whether the damage is caused by contusion, laceration, or compression by bone, hemorrhage, or edema does not exist. The urgent indications are for "spinal decompression" by laminectomy with free opening of the dura, giving the cord fibers the best possible opportunity for repair. (See Case III.)

One stated objection to the early operation, or in fact to any operation in the absence of deformity, is that in many reported cases of early laminectomy little or no improvement followed, though no displaced bone was found; "and as the cord appeared normal, the dura was not opened." Such observations are similar to those regarding so-called cranial decompressions when the dura is not opened.

Compression of cord fibers by edema will not be relieved by the removal of the laminæ alone. And just as in head injuries, removal of bone will not relieve the intracranial pressure unless the dura is also opened, so in spinal fractures a free opening of the dura is most important and should always be done.

J. T. Bottomley advises in partial lesions of the cord that "if fingers or the roentgen-rays find no deformity of bone, then it is

fair to assume that lesion is due to contusion, hematomyelia, or hematorrachia, and operation is not indicated," as "the blood will be absorbed in four to six weeks." But as cord fibers, if damaged and compressed, may degenerate in four days, the pressure of the hemorrhage present, augmented by the following edema, may cause irreparable damage to the injured fibers, and probably also to many sound ones, long before the blood clot is absorbed.

E. W. Taylor, who also says that the damage to the cord is immediate following the injury, and that delay in operation is advisable, reports a case, and exhibits the cord of a large extradural hemorrhage, with organization of clot and resulting compression, of which he says "that operation would have been of benefit." Then why advise delay until the cord is irreparably damaged, as a wait of only four days may cause degeneration of the compressed fibers.

Bottomley also says that in partial lesions of the cord, if after waiting (weeks or months) no improvement occurs, or if improvement occurs and then ceases or retrogrades, operate. And yet what can be done by a late operation, in the face of continued compression of the cord by bone, hemorrhage or edema, or by all three, over a long period of time that could not be better done and with more chances of benefit by an early operation? Case IV is an excellent example of this.

It is said by many surgeons that early laminectomy adds insult to an already damaged cord, and yet these surgeons advise in midcervical fractures, with danger of involvement of the fourth cervical segment, immediate operation to prevent respiratory troubles.

Immediate loss of power and sensation in parts of the body below the fracture points to laceration of a section of the cord. Here the indications are for an early operation not for the sake of the destroyed fibers, but with the view of warding off the compressive effects of the fast following edema, thus preserving the sound fibers and giving the best chance of recovery to the damaged but not destroyed fibers.

There are, however, many cases of a milder type in which there is no immediate loss of function. In these cases following the injury there are cramps in the legs, burning and tingling of the skin of the legs, followed by a progressive loss of power and sensation. In these cases the symptoms indicate not laceration, but compression of the cord by bone or hemorrhage.

The progressive march of the symptoms show, not a further narrowing of the bony canal, but an increase of the hemorrhage and arrival of the destructive edema. Here early laminectomy is imperative if we would save the cord, or parts of it, from permanent injury. Even if no hemorrhage is present there may be a backward dislocation of the vertebral body, so that the cord is "kinked"

and the canal narrowed; even if it is impossible to remove the bone projecting into the canal the laminectomy gives the cord ample room to curve over it, and allows for the escape of inflammatory exudate. Case II well illustrates this "kinking" of the cord by a displaced vertebra. Operation should be done as soon as the symptoms of shock have passed away. Even if the symptoms of cord injury are but slight, if progressive, laminectomy should be done and the dura opened to allow of drainage of whatever hemorrhage may be present and to ward off by this spinal "decompression" the effects of the edema which invariably follows injury to the cord, and which is so destructive to the delicate fibers.

Fracture with Symptoms of Immediate Complete Abolition of Function. It is in this type of cases that the opinion of surgeons is most sharply divided as to the advisability of operative interference. Many hold that immediate complete motor and sensory paralysis, with abolition of all reflexes below the lesion and loss of sphincter control, shows a total transverse lesion of the cord, and laminectomy is unjustifiable and can do no good. This would be true did the above symptoms positively indicate, as they do in many cases, complete destruction of the cord. But there have been many cases reported in which all the above symptoms were present, and were considered complete lesions of the cord, in which later partial function returned even without operation, and many reported in which operation was followed by fair recovery. The Bastian-Bruns so-called law, which is that there is a total loss of tendon reflexes in complete lesion, is, as an aid in diagnosis, only of value in a negative sense. That is, the presence of reflexes makes it certain that there is not a total lesion, while the absence of reflexes is not proof that the lesion is total unless such absence is persistent. In many cases of partial lesion there is a total loss of reflexes for more than eight days; so that there are no symptoms short of a deformity at the site of injury so great as to show complete obliteration of the spinal canal, which prove a complete transverse lesion of the cord.

It has been regarded by many that complete abolition of function below the injury must indicate, if not laceration, at least most severe compression of the cord. This is by no means necessarily the case. Alan Newton has shown by experiments in animals that the spinal cord is extremely sensitive to light degrees of compression. He found that a glass rod gently placed on end on the exposed cord arrested conduction immediately. After removal of the compression, conduction returned after an internal varying directly with the duration of the compression, and the amount of interference with function remaining after eleven to fourteen days following experiment depended on the same factor. These results of Newton's experiments are in themselves a strong argument for the early operation, showing the beneficial effects of swift removal of pressure due to whatever factor.

Mixter and Chase report a case of fracture of the 4th, 5th, and 6th cervical vertebræ, with immediate symptoms of complete destruction of the cord. Operation was done twenty-four hours after the accident. Six days later sensation returned over the entire body. In two weeks there was some return of the reflexes and the patient finally recovered fair control over the bladder and fair use of the legs. Died one year after injury from pyelonephritis.

Guy Hinsdale reports a case of a woman with fracture of the 1st, 2d, and 3d dorsal vertebræ, and complete and immediate paralysis of the body below the nipples. Laminectomy four days later showed the cord was edematous and pink, and much fluid escaped. Three years later the patient could walk with assistance, had control over the bladder, and touch sense was normal on one side. It is the added pressure of this edema, as found in Hinsdale's case, that is so destructive to nerve tissue, and which is present after every cord injury, that may turn the scale and cause widespread destruction of the cord, and furnishes a chief reason for early operation.

Many surgeons hold that in the absence of bony deformity, as determined by the fingers and the roentgen-rays, and with complete abolition of function, while it does not prove complete destruction it is better to delay operation until the cord has had an opportunity to recover what power it can; and when improvement ceases to operate.

C. G. Cumston states as an aid to diagnosis that reactions of degeneration are absent in the paralyzed muscles in even severe compression as long as the fourteenth day, but if the cord is completely severed there is no excitability of nerves to the induced current after the fourth day. But this is of little value from the stand-point of treatment, for under severe compression, increased by the certain edema, the cord, certainly the damaged fibers, will degenerate in four days.

Bastian, Kocher and others have outlined symptoms which indicate complete lesion of the cord, but the cases described above and many others show that these symptoms do not prove destruction of the cord, and we cannot rely upon them. Kocher believes that operation is unjustifiable in case symptoms of complete lesion are present, and favors operation in partial lesion when symptoms have come to a standstill. But, as we have seen, the symptoms of complete lesion are not absolutely trustworthy, and delay in partial lesion may irreparably damage the cord. A much more rational stand is that taken by Dr. Walton, who says:

"Early operation will not only accomplish all that later operation will do for these cases, but will do it better." (See Case X.)

In my opinion early laminectomy in skilled hands is the best treatment by far in fracture of the spine with cord lesions, and the only contra-indication to operation is a bony deformity so great

as to show beyond doubt that the spinal canal is obliterated and the cord hopelessly crushed.

The operation should be performed as soon as the patient has reacted from the shock and the site of the lesion localized. A free opening of the bony canal will relieve compression by bone, whether due to driven-in laminæ or a backward projecting vertebral body causing angulation of the cord. If a projection presses against the cord in spite of the removal of the laminæ, sufficient bone can be chiseled or rongeured away to give the cord ample room. A free opening of the dura will permit of removal and drainage of blood, and will offset the compression effects of the following edema. The dura may be re-closed or not, as indicated by the condition of the cord. In very many cases it is best left open. The technic of the operation is briefly as follows:

A single incision is made in the median line down to the tips of the spinous processes. The muscles are then incised close to the spinous processes down to the laminæ and the incision packed with hot wet gauze to check bleeding. This is then done on the opposite side and also packed. The laminæ are freed of muscle by a broad periosteal elevator the whole length of the wound on either side. A large self-retaining retractor is then inserted, which gives a good exposure and effectually prevents bleeding. The ligaments between the spinous processes are divided and the processes removed by large special rongeurs. The laminæ are now rongeured away out to the transverse processes, thus giving a good exposure of the canal and cord. The dura is always to be opened, and in many cases it is best to leave it at least partly unclosed. Opening of the dura and the arachnoid allows for escape of blood or edema, and if the cord is tense and swollen a small longitudinal incision in the posterior columns will afford drainage. A drain at either end of the wound extending to the dura, or at least to the bottom of the muscle wound, will provide an escape for the wound fluids. The wound is closed by a layer suture of chromic catgut and the skin with silk. A narrow posterior splint of plaster moulded to the spine will prevent movement of the trunk and give the patient much comfort. Drains and some sutures are removed on the second day and the remainder in five days.

What shall be done in those cases in which at operation the cord is found completely divided? It is almost generally agreed at the present time that cord fibers once severed do not regenerate. Murphy said that if the cord is severed, approximation will avail nothing. However, of the five cases reported of severed cords sutured, four were living several years after operation, while without suture no patient has lived over one year. The great improvement following suture, in the sensory and trophic disturbances, thus averting the terrible bed-sores, warrant suture for this alone. The writer believes that suture of a severed cord should be attempted,

If the ends cannot be approximated and the lesion is in the dorso-lumbar region an attempt should be made to unite the roots above and below the lesion, as suggested by Kilvington. This cannot be done in the upper dorsal or cervical regions because of the short course of the roots in the canal. (As examples of complete lesion see Cases VIII and IX.)

There are many cases seen of old fracture with cord lesion on whom, for various reasons, no operation was done or the operation was not completely successful. They present symptoms varying from simple foot-drop or spasticity of one extremity to paralysis with loss of bladder control. Many of these show increasing impairment of function due to late scar-tissue formation and collecting of fluid at the site of the lesion or to new bone growth. Many of these cases can be improved by operation even at a late date, and in some a brilliant result is secured. (See Case VI.) These patients should not be abandoned as hopeless cripples merely because a period of several months or even years have elapsed since the injury was received. Although operation will completely relieve but few of them, yet definite improvement may follow laminectomy even at a late date.

However, the many cases reported of benefit resulting from late operation when symptoms of progress cease or retrogression sets in only indicates the good that could be done by early operation, for the factors of continued compression, bone, hemorrhage, or edema that brought improvement to a standstill had certainly worked harm that would have been prevented by early operation. (See Case VII.)

Therefore, I believe that in every case of fracture of the spine with damage to the cord, excepting only complete obliteration of the bony canal, an early laminectomy is urgently indicated to relieve the cord of the damaging effects of bone-pressure, hemorrhage, and edema, and to give the nerve tissue the best possible chance for repair.

SUMMARY. *Reasons for and Advantages of Early Laminectomy.*

1. Relieves pressure from cord whether due to depressed bone or blood clots.

2. If fracture-dislocation, allow cord ample room, relieving pressure effects of angulation.

3. Provides drainage of the certain edema, which by its compressive effects is destructive to the nerve fibers.

4. Allows for drainage of hemorrhage, if present, the compressive effects of which may be so great as to permanently damage the cord.

5. In skilled hands, laminectomy is not a difficult or dangerous operation, and by doing it early the surgeon has given the damaged cord the best possible chance for repair.

The following cases, some of which were operated on in con-

junction with Dr. William Sharpe, were selected as illustrating points emphasized in the text:

CASE I.—Fracture dislocation of the 2d cervical vertebra without cord injury. No operation.

W. K., aged twenty years, fell two stories, striking on his head. Unconscious for a short time. Took a walk one hour after injury. Continued to work, with occasional pain in the head, otherwise no complaint. There was a definite deformity of the spinous process of the second cervical vertebra, and the roentgen-rays showed a fracture-dislocation of this vertebra. A plaster collar was applied and worn for some time. The only complaint at this time was some numbness and tingling of hands and legs. Reflexes were normal: no Babinski, no sensory disturbances, and no sphincteric trouble. Three years later he still was well.

CASE II.—Fracture-dislocation of the first lumbar vertebra with angulation of the cord.

P. M., aged forty years, fell from a hand car, striking his back. No loss of consciousness, but he was unable to rise, and his legs felt numb and cold. Had pain in the dorsolumbar region of the spine, occasionally radiating into the thighs. Retention of urine. Seen two weeks later. Could flex and extend both legs weakly. Hypesthesia over both legs to the groin; no analgesia. The reflexes of the lower extremities were entirely absent and the abdominal reflex absent, but the epigastric was present. No Babinski or Oppenheim (rather remarkable). There was a marked "knuckle" of the spine, with displacement of the first lumbar spinous process one and a half inches to the left of the median line.

Operation. Laminectomy was done, removing the laminæ of the 12th dorsal and the 1st and 2d lumbar vertebræ. The first vertebra was found rotated to the left, so that the spinous process was one and one-half inches from the median line. The right lamina of this vertebra was fractured and separated from the spinous process. A mass of torn ligaments, muscle, and blood clot found in the space between the spinous process and fractured lamina pressing down upon the cord. The cord was sharply angulated by the projection backward of the dislocated 1st lumbar vertebra. The dura was freely opened and the arachnoid found balloned with fluid and the cord edematous. No hemorrhage was found. The dura was partly re-closed and rubber tissue drain passed down to the cord. The wound was closed by a layer suture of chromic catgut and a narrow posterior plaster splint applied; thirty-two days later he was walking with aid of crutches. Sensation was normal. Knee-jerks were still absent.

One year after operation he walks with spastic awkward gait, but without crutches or cane, and is able to work.

CASE III.—Fracture of the lumbar vertebræ, with dislocation of the 3d lumbar.

P. P., aged twenty-seven years. Struck by an automobile. Brought to hospital in shock. Not unconscious. Could not move legs, but one hour later moved them slightly. Reflexes absent and hypesthesia to groin. Retention of urine. A definite depression found over the 3d lumbar vertebra. The spinous processes of the 2d and 4th lumbar vertebræ were palpable, but crushed into the laminæ. Had deep laceration of the perineum and sacral region. Laminectomy was done as soon as the patient reacted from the shock, several hours after the injury. The spinous processes and laminæ of the 2d, 3d, and 4th lumbar vertebræ were removed, disclosing a backward dislocation of the 3d vertebra, which reduced itself with a definite click and the rongeurs were inserted under the laminæ. There was a marked angulation of the cauda opposite the 3d lumbar vertebra. The dura was found distended and tense, but not torn. On incising the dura, blood-tinged fluid spurted to a height of seven inches. No definite subdural hemorrhage was found and no apparent lesion of the roots of the cauda. Dura partly re-closed and the wound closed by layer suture, with one drain at the lower angle. Recovery uneventful, though the laceration on the sacrum required dressing for two and a half months; patient fully recovered, and one month later walked with crutches. At the present time, fifteen months later, he is working and has no complaints. Babinski on left foot.

Case IV.—Old fracture of spine.

J. S., aged forty-two years; miner. Eighteen months previously, while mining, was struck on the lower back by falling rock. Not unconscious, but could move his legs only slightly. Was in hospital eight weeks; diagnosis: "sprain of back that would get well in time." No operation. Has since been unable to walk without crutches. Ever since leaving hospital has had pain, intense at times, in feet and legs. Retention of urine for eight days following accident, and dribbling for last four or five months. Examination eighteen months after accident showed exaggerated reflexes in lower extremities; a variable Babinski was more often present on the right side and scattered areas of hypesthesia and hyperesthesia on both legs. Both legs were spastic, with slight ankle clonus on the right side. Can move legs but weakly. Roentgen-rays showed deformed vertebræ at the lumbosacral junction.

Operation. Spinous processes and laminæ of the 4th and 5th lumbar and 1st sacral vertebræ removed. The bodies of these vertebræ were found crumpled together, with marked posterior displacement of the 4th lumbar vertebra, a portion of it protruding backward among the roots of the cauda, almost separating it in two portions. The dura opposite the 5th lumbar vertebra was thickened with many underlying adhesions, with a definite angulation of the cauda at this point. The adhesions were freed, the projecting portions of bone cut away and the dura re-closed. The wound was

closed by layer suture of chromic catgut and drained by rubber tissue. Three days later he spoke of peculiar sensations in the toes and feet. Six months later he was doing light work in the mines. At present is doing work which requires standing, although not heavy work, using neither crutches nor cane.

Here an early laminectomy would have relieved the compressive effects of the fractured vertebræ and prevented the eighteen months' invalidism of the patient.

CASE V.—Fracture of the 1st lumbar vertebra.

R. L., aged four and a half years. When nine months old was struck by an automobile while lying in her coach. Since then she has been unable to use her legs and has had incontinence of the bladder and bowel to the present time. Examination at four and a half years showed slight motion in toes and feet, but they cannot be raised from the bed. Sensation only slightly impaired; no anesthesia or analgesia. Quite marked left dorsolumbar scoliosis.

Operation. The spinous processes of the 12th dorsal and 1st and 2d lumbar vertebræ were removed, revealing a marked posterior constriction of the spinal canal by the laminæ of the 1st lumbar vertebræ. The dura was opened, exposing a cord apparently normal. No evidence of hemorrhage or of scar formation. The dura was re-closed and the wound closed by layer suture.

No improvement noted as yet, six months after operation. In this case it is probable that permanent damage was done to the cord at the time of the accident. However, early operation would have removed the compression of the fractured laminæ and offset the following edema, and possibly preserved to her more function than shw now has.

CASE VI.—Old fracture of lumbar vertebræ.

C. M., aged eighteen years. Fell from a second-story window, striking on the back. Not unconscious. Unable to move the right leg. Roentgen-rays showed dislocation of the 2d lumbar vertebra. No operation. Plaster cast applied for two weeks. Unable to use the right leg. After one month the patient could walk with crutches. No bladder symptoms or sensory disturbances. As months went by some improvement occurred. She could walk without crutches, but with marked dragging of the right leg.

Examination six months after accident showed much atrophy of the right leg, especially in the extensors of the thigh. Slight foot-drop. Patient walked on the toes of the right foot and dragged the leg badly. No Babinski, Oppenheim, or clonus present. No disturbances of sensation. Definite hump on the back over the 2d and 3d lumbar vertebræ. Roentgen-rays showed dislocation to the left and possible fracture of the 2d and 3d lumbar vertebræ.

Operation. Median incision over the first four lumbar vertebræ. Spinous processes and laminæ of the 2d and 3d vertebræ removed, disclosing much scar tissue beneath. Body of the 2d lumbar pro-

jected backward, causing angulation of the cauda to the left. On incising the dura fluid spurted several inches. Roots of the cauda were found compressed between the scar tissue under the laminæ and the dislocated vertebræ. Removal of laminæ allowed ample room for the cauda. The dura was partly re-closed. Rubber tissue drain inserted and the wound was closed by the usual method.

Thirty days after operation patient has better use of the leg and walked with improved gait. Four months later there was marked improvement, which has continued to the present time. Ten months after operation patient walks with but slight limp, though there is still some weakness in the dorsal flexion of the foot.

CASE VII.—Old fracture at dorsolumbar junction.

Mrs. J. C., aged forty-two years. Seven years ago fell on a step, striking the lower part of the spine. Immediately got up and walked for some distance home without much pain or difficulty. No symptoms until three months later. Then had difficulty in urination, which passed on to incontinence. The bowels became affected a short time afterward. At the same time there was twitching of the muscles of the left leg, and later partial paralysis of this leg with foot-drop developed. Eighteen months later the leg improved and partial paralysis with foot-drop developed in the right leg. She still dragged the left leg, but the right leg was the weaker. For the last five years she has been unable to walk alone.

Examination seven years after accident showed considerable motor power in the left leg, but drags the right leg and cannot stand alone. Pateller reflexes much exaggerated. Babinski on both sides and ankle clonus marked R>L. Slight but constant muscular twitching of the right leg. Hyperesthesia over both extremities, abdomen, and back. Considerable muscle spasm over the buttocks in response to stimuli. Serum and fluid Wassermann negative. Roentgen-rays showed thickening of the 12th dorsal and 1st lumbar vertebræ.

Operation. Median incision from the 11th dorsal to the 2d lumbar. Laminæ of the 12th dorsal and 1st lumbar enormously thickened, one-half to one inch in thickness, very vascular, spongy bone (callous formation). Beneath these laminæ was found a mass of scar tissue, one-half to three-fourth inches thick, pressing upon the cord and causing depression in the dura. On removal of this scar mass the dura rounded out; the cord appeared normal. The wound was closed in the usual manner; no drain.

Three months later there was a variable improvement noted; better some days, others not. Seven months later the patient could walk without support and with but slight spasticity. After riding 135 miles in a Ford car she was able to walk into the office. There is still present a double Babinski and vesical incontinence.

CASE VIII.—Fracture of the 10th dorsal vertebra with complete lesion of the cord.

T. S., aged thirty-four years. Fell a considerable distance and was brought to hospital conscious, but with complete paralysis of the legs and all reflexes abolished. Anesthesia of both legs up to the iliac crests. Hypesthesia over area of the 12th dorsal segment one and a half inches above the ilium. Retention of urine. There was an easily palpable prominence of the 10th dorsal vertebra. Laminectomy was done when the patient had reacted from the shock, twenty hours after accident.

Operation. Median incision from the 9th to the 12th dorsal vertebræ. The interspinous ligaments were found torn loose between the 9th and 10th vertebræ. There was a posterior dislocation of the 10th dorsal vertebra, causing a marked angulation of the cord. The dura was tense and bulged through the laminectomy opening. The cord was immensely swollen and completely filled the dural sac. On opening the dura, blood-tinged fluid escaped and the cord appeared macerated, more in its left half, with small hemorrhages scattered over the surface. As the cord bulged markedly the laminæ of the 9th and 8th dorsal vertebræ were also removed and the opening in the dura was enlarged. There was no definite separation of cord fibers. The dura was left unclosed and the muscle wound closed in the usual manner with a drain.

Operation disclosed a severely damaged cord, but by relieving bone compression and by offsetting the pressure effects of the severe edema, gave the fibers the best possible chance for repair. Unfortunately on admission to hospital patient was catheterized by an orderly and developed a cystitis which caused his death eighteen days after operation.

In cases of cord injury it is wise to avoid, if possible, the use of the catheter. Repeated massage of the bladder sphincter through the rectum will usually relieve retention.

Case IX.—Fracture of the spine with complete lesion of the cord.

W. O., aged thirty-eight years. While intoxicated the patient, a very heavy man, fell backward from a fence to the ground. When brought to hospital he seemed to be merely drunk, but application of ammonia to the nose caused him to move his arms, but not the legs.

Examination of the back disclosed a definite hiatus over the 10th dorsal vertebra. When the effects of the alcohol had passed he was found to have complete paralysis and anesthesia of both legs to the waist. Complained of severe pain in the back over the lower dorsal spine. Laminectomy was done twenty hours after the accident.

Operation. Incision from the 8th to the 10th dorsal spines. There was a definite posterior dislocation of the 11th dorsal vertebra, with fracture dislocation of the 10th dorsal. On removal of the laminæ of the 9th, 10th, and 11th vertebræ much free bleeding was encountered in the region of the 10th dorsal vertebra, which was

so severe as to require packing. On incising the dura much free blood escaped, revealing a complete separation of the cord for a distance of one and a half inches. The 10th dorsal vertebra was freely movable. Packing was required to control the hemorrhage. The dura was left unclosed. A drain was inserted and the wound closed by the usual method.

The symptoms in this case from the outset were those of complete cord lesion, but in laminectomy lay the only possible chance for relief. An attempt to suture the cord, or to unite the roots above and below the lesion, was rendered impossible by the extensive hemorrhage.

Death occurred on the twentieth day, this patient having also developed cystitis following unwise catheterization.

Case X.—The importance of accurate localization of the lesion and its difficulty in the absence of definite symptoms, especially in children, is well shown by the following case:

J. B., a child, aged seven years, suffered a fall, which showed no deformity of the spine, but caused complete paralysis of the legs and sphincter. Laminectomy done two days later over the 6th and 7th dorsal vertebræ showed no lesion of the cord. Seen by me seven months later the paralysis of the legs and sphincters had persisted in great part. The lesion was localized over the 3d dorsal vertebra. Laminectomy at this point showed slight thickening of the laminæ. Many adhesions between the cord and meninges, the large amount of fluid in the meshes of the adhesions giving it a cystic appearance and much yellowish scar tissue present (old hemorrhage). There has been, as was to be expected from the conditions found at operation, no improvement in this case, nine months after operation.

Early operation at the proper site would have removed the blood, offset the effects of the edema, and would doubtless have been of much benefit.

THE ETIOLOGY AND PREVENTION OF TUBERCULOSIS FROM THE SOCIOLOGICAL POINTS OF VIEW.

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The etiology of tuberculosis has not yet been solved. For thirty-nine years, since the wonderful discovery of Koch, we have known that no tuberculosis exists without the tubercle bacillus. This one great truth has been established, but it is not all the truth, for it is just as salient to say there is no tuberculosis without the animal body. Even these two great factors do not close the discussion,

for some relation arises between the tubercle bacillus and the animal body, occasioned by their contact, which must attain before the essential feature of tuberculosis, the miliary tubercle, is formed.

The Tubercle Bacillus. From the time of the isolation of the tubercle bacillus by Koch, it has been studied in many ways. We know in part its form, singly and in colonies, its varieties, its chemical reactions and chemical compositions, its necessary food and environment, its excretions and enzymes, its life history, in glass and as a parasite, its resistance to light, to heat, and to chemicals, but not yet the one essential factor, why and how it produces a tubercle.

The Animal Body. The study of the tubercle bacillus outside the body has been comparatively easy. The organism is, however, lost when we put it within the animal body. We know it soon enters a phagocyte cell, probably chiefly one of endothelial origin, but once inside of this cell, there begins a series of chemical and physiological changes, wholly obscure to us as yet. After some days, however, we see the evidence in the miliary tubercle, of the busy life it has led, marshaling against it at least three different armies of cells: polynuclear leukocytes, endothelial cells, and lymphocytes.

It is not surprising that our knowledge of etiology as it relates to the animal body is limited, for if we seek to reduce our size to that of a tubercle bacillus, retain our mentality, and start a wandering journey within the animal body we are soon lost in a maze of possible resting places. Before starting on such a journey we have the choice of several portals of entry, each leading to an environment in different organs and tissues of widely varying chemical structure. We see a chance of destroying sight with almost instant discovery, by establishing a solitary tubercle in the optic nerve, as opposed to the chance of establishing many thousands of tubercles, without discovery, within the lungs, or in a hidden lymph gland. But such choice of a final resting place is destroyed by the obstacles we meet on our journey, a blood current to carry us here or there, a wandering cell to transport us, a fixed cell to engulf us, an inimical fluid to dissolve us, it is small wonder all the truth has not yet dawned.

Our difficulties grow when we realize that we are just establishing our first firm basis for accurate physiological and chemical study of the animal body. Through the efforts of Fischer, Hoppe-Seyler, Folin, Mendel, Starling and many others we have realized that, first, an equilibrium must be established for the animal body, and, after this, an intake of known composition be added before resultant compounds can be determined. It is not strange when this knowledge is so meager that we have not discovered under what chemical condition of the body the tubercle bacillus can flourish.

Investigator and Investigation. One of our best students has recently said to me, "If I had the opportunity to study tuber-

culosis I would not know where to begin; it is like battling against the waves of the ocean." It is not so bad as this, however; what we need is a new grasp of our problem on a broader basis. The crux of the problem is the relation existing between the tubercle bacillus and the animal body.

New problems for research are opened to us daily by the surgeon, the anatomist, the physiologist, and the chemist, and probably many of these must be solved before the true etiological factors are apparent and relief from our suffering from this disease attained.

PRESSING PROBLEMS. Such problems are involved in the answers to the following questions:

Why does the tubercle bacillus select the apices of the upper lobes of the lungs in man and the cephalic ends of the caudal lobes in cattle?

What is the relation of small doses of tubercle bacilli from various sources to later immunity and a reduction of morbidity and mortality?

What is the relation of early localized lymph glandular lesions to later more generalized tuberculosis, ranging from early lesions in the lungs to general miliary tuberculosis?

What is the chance of reaching the tubercle bacilli lying within tubercles in the body of an animal by chemicals introduced into the blood stream, and what hope does such study hold out of cure or arrest of the process?

What bearing has the physiology of various organs, such as the spleen, on the general problem of immunity to tuberculosis?

What hope have we of establishing immunity by vaccination or arrest and cure by immune sera? and so on, a host of unanswered questions bearing directly on our relief from the stand-point of control by social measures.

If we choose the lung as the chief point of attack in the animal body as the object of our study, we are conscious at once of a chemical factory to which every organ and tissue sends its contributions, through veins, lymphatic vessels and thoracic duct, contributions which vary all the way from the internal secretion of the adrenal glands to the neutral fats, changed by the lining membrane of the bowel and transported by the lymphatic channels from the food in the intestine.

Any one of these substances may contain the solution of the secret of the choice of this organ by this widely distributed bacillus.

If we seek to solve the question why tuberculosis attacks the apex of the upper lobe in man, one can see how complex even this question is when the following explanations of it are available for study.

1. That it may be due to mechanical pressure from rib and clavicle producing a quiet area; this, of course, is not applicable to the place of choice of the bovine lesion in the caudal lobes.

2. There may be a peculiar chemistry of the apices of the lungs in these two animals dependent upon position and directness of the blood stream or other similar factor, determining a peculiar quality of fluid or cell in this region.

3. There may be some peculiar anatomical relation existing between the portal of entry, the lymphatic glandular system, and various arteries which, by directness of stream and current, carry tubercle bacilli once entering the blood to these regions.

4. There may be some anatomical relation between the lymphatic system and these regions which carries to them tubercle bacilli entering the lymphatics.

Let me point out again the difficulties by taking the latter as an example. Only within one year has there been any accurate knowledge of the lymphatics of the lung and their relation to the intestinal lymphatics, and yet there seems much of evidence to prove that the tubercle bacillus has some definite relation to the endothelial cells of this vascular system.

These problems may be solved for us by the chemist, the physiologist, the surgeon, or by all combined.

What we especially need are funds and facilities to provide the opportunity for research and research workers to take up these problems.

THE SOCIAL AGENT. Our lack of specific knowledge can in no way be offered as an excuse for laxity in putting in operation the knowledge we already possess. Our various organizations (from national to local), the most efficient ever established against a single disease, stand as evidence that we have not shirked our duty.

Perhaps, however, our wisdom has not always been as prominent as our energy, and mainly we have failed to realize that our most efficient agents must always be doctors and nurses with a social sense. These alone can combine skill in diagnosis and treatment, with a knowledge of social conditions which underlie the spread of this disease.

One of the most disturbing features of modern work has been the gradual loss of respect for medicine and nursing as professions. This has become especially marked in tuberculosis work, where, with the establishment of laboratories, new agents of social service, and executive secretaries of organizations, the curious condition has arisen that there is a wide-spread opinion that little skill is necessary for the diagnosing and provision of consumptive people. There is scarcely a city or State today in which a layman operating as secretary or agent of a society for the prevention of tuberculosis is not able to both get the sputum analyzed and the patient placed in a hospital without ever having to see a doctor.

I often wonder whether our whole flimsy construction of medical and nursing training is not at fault when it is possible for laymen and laywomen to do the work which our present long course of training leading to degrees, licenses, doctors, and nurses to do.

Two great facts for some years have steadily robbed the race of the assistance of these two groups: (1) the exclusion of tuberculosis from the institutions of general professional training, and (2) the establishment of special institutions in territory inaccessible to students of these two great professions.

A new and healthy movement in America has lately been evidenced by the work of the Tuberculosis League in Pittsburgh, the Phipps Institute in Philadelphia, and Jefferson Medical College, in connection with the schools to which they are attached, in demanding practical experience in this work as part of the prescribed course.

I am convinced that the single factor of making the practical education of tuberculosis, from the stand-point of diagnosis, treatment, and social aspect, a demand of the prescribed courses for doctors and nurses in the institutions where they are trained will do more in five years to reduce the morbidity and mortality from this disease than all the special institutions for its care that we have been at such pains to establish.

THE SOCIAL FABRIC. How much of tuberculosis is closely bound up with our houses, our schools, our food, our workshops, our means of transportation, our dusty streets, our wages, our poverty, and with disease other than that caused by the tubercle bacillus, cannot yet be answered completely and finally. We know enough, however, to make these relations part of the education of our whole population.

For such education three great sources are always open to us:

The first and most important—the schools—is most likely to succeed because of the legal backing which makes listening and teaching compulsory.

The second, the pulpit. I never attempt a special lecture on this subject that my effort does not sink into insignificance beside those of my friends and coworkers in my own community. For instance, when Rabbi Levy, with his wonderful conception of the Fatherhood of God; Bishop Canevin, with his great and good paternalism; and Dr. McIlvaine, with his fearless and loving admonition, and many others, join on a chosen Sunday each year in teaching the truths of this great problem to their congregations I realize that a force for education has joined the ranks of our special organizations the world over that marks a most powerful ally in the direction of universal education of this subject.

The third great agent of education is the daily paper. I think all who know must feel disappointment with the help of these powerful agents. I suppose their sin is wrapped up with the fact that their papers must be sold. The selling agent is news, and not the reiteration so essential to education; but every once in a while the entrance of tuberculosis to the family of the throne room of the paper brings forth a new ally of wonderful power.

The essential feature of such education, however, must be truth. Each day reveals new evidences of sadness resulting from careless statements which lead only to fear and bring the suffering of the outcast to the consumptive populace.

The standardization each year of knowledge through some central office, like the Federal Government or the National Association, would tend to lessen the dangers of each successive period of advance.

Correlated Movements. Next to education there is not a movement for the health and welfare of the race which has not had its share in reducing this sickness—housing reform, child welfare, pure water, better wages, pure food, health laws, school lunches, ventilation, food lines—all aid.

I often wish to each might be given the credit for all it has contributed to the present great reduction in tuberculosis, for I sometimes fear that in our enthusiasm we have claimed too much and been misled by the establishment of institutions which, while necessary for housing this excluded portion of the race, have largely failed to rise above mere housing institutions and have neglected that perhaps more important foundation, provision for specific research in this work.

Perhaps one of the most striking conditions of modern municipalities is the large number of small charitable institutions, each with laundry, kitchen, bakeshop, purchasing department, engineering department, and high-priced superintendent and officers, to which the whole public gives more or less lavishly without any thought for economic and careful use of their funds. There ought to be some place, a legal authority, to stop such waste and carelessness and establish a central department, including laundry, kitchen, storehouse, and other such necessities for these smaller institutions for each community.

Many interesting social studies by Federal, State, and local organizations have been made. Among these are the housing surveys by Dr. Biggs in New York, the study of the children of the tuberculous, as compared with the children of the non-tuberculous and many others which need confirmation, with the eradication often of sources of error in the comparison of results which arise because of variation in technic.

Division of Labor. With such a universal problem and so great a host of agents entering into its solution, perhaps the two outstanding demands of this work are uniformity and equable division of the labor.

To what end is all our labor if one class is helped and another neglected; if one State is efficient and another lax; if one race is protected and another left to exposure?

As it appears today the poor receive a large percentage of our beneficence while the great middle class suffers for its independence

by our neglect, and the rich wander from climate to climate and doctor to doctor, hoping that God in His goodness has vouchsafed some knowledge for their benefit which can be purchased with gold and silver to the exclusion of the rest of the world.

Or, again, one State provides lavishly for this one feature of public health while a neighboring State, separated from it by an imaginary line, turns its back upon its duty; or one town attempts efficient handling of its problem while a nearby borough does nothing. The source of such discrepancies, of course, lies where the law originates in the State and Federal Government.

Relation to Other Health Movements. When such a law is at last prescribed we are apt to make again the mistake of separating tuberculosis from other health and charitable activities, and so waste a great part of the efforts of our agents by reason of a duplication of labor.

The Solution. I am more and more convinced of the soundness of the solution for this problem which I have offered on more than one occasion, and inasmuch as I believe in it so fully, I am to be guilty of proposing it again to you.

This plan is based on a study of our solution of a similar universal problem presented by our educational demands.

Emanating from State law there is in general established in educational work a unit equipment for a unit of population. By this equipment is gained a uniform compulsory and intensive application of the law to all concerned. The money for the expense of this care is provided by State and local taxation, determined largely by the density of population and the need of the community. Those who are interested in this phase of the question would do well to read Cubberly's *Problems of State and Municipal Education.*

In the educational field there has gradually developed a knowledge of the equipment necessary for a given population, and this equipment has been apportioned so as to be easily accessible by those whom it is to serve. The management of these units is centered in a legally constituted governing body, which also controls the expenditure of the funds collected by taxation.

The same form of control is applicable throughout to tuberculosis and other health problems.

In the first place, our statistical studies have given us fairly accurate knowledge of where to place our equipment and of what the equipment should consist.

I should say that for each hundred thousand population there should be a hospital of 200 beds, a dispensary and an open air school. There should be fifteen nurses, of whom five are visiting social service nurses and four or five physicians. Such an equipment might easily expand and include all public activities, child welfare, pneumonia, syphilis and other health and public welfare problems.

The expense should be borne as the educational expense is borne, and the demand made mandatory by state law.

Large centers of population would be looked on as but the multiplication of units of 100,000, and the equipment would be multiplied accordingly, just as we now multiply our school equipment. Each unit would be self-governing, but centralized in some central governing board which would establish the uniformity of the work and the prevention of overlapping.

The State that sees fit to establish such a principle will, it seems to me, soonest reach the land of heart's desire, and will have a machinery as elastic as the problems to be dealt with, a machinery that can grow as knowledge grows and retract or reconstruct as necessity decreases, a machinery that can be used as a teaching center for doctors, nurses, and social agents, and the sooner it comes, the sooner will we see spelled on the wall the doom of our present boarding houses for sick and well consumptives, and waste of effort.

THE RELATION OF TUBERCULOSIS OF THE BRONCHIAL GLANDS TO THE DIAGNOSIS AND TREATMENT OF TUBERCULOSIS OF THE LUNGS.

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It is beginning to seem more than probable that the first chapter in the story of tuberculosis of the lungs is often written in the bronchial glands, and that if this chapter could be discovered and understood as it is being written in the bronchial glands, that we might prevent the writing of the future chapters in the lungs. This is strongly suggested in those cases characterized by the prodromes of tuberculosis which cannot be confirmed by physical examinations of the lungs: the "pretuberculous cases"—what the French have called "tuberculizable"—cases seeking an examination because there is a history of tuberculosis in the family, or a cough, or the syndrome of tuberculous toxemia. It is precisely in these suspicious cases, when we are unable to find any evidence of tuberculosis of the lungs, that we should remember that all these suspicious prodromes may come from the bronchial glands, and that our search for tuberculous processes is only half-made when we stop with the lungs and do not include the bronchial glands.

Cases of tuberculosis of the bronchial glands without physical signs of tuberculosis of the lungs are dangerous, because they may at any time prove fatal by perforating the trachea, bronchi, esophagus, or bloodvessels, by inducing pathological changes in the lungs

which furnish favorable conditions for the growth of tubercle bacilli, and by the direct extensions of tuberculous processes in the bronchial glands into the lungs.

The pressure of enlarged tuberculous glands upon the trachea or bronchi may so compress their bloodvessels that engorgements result in rupture with hemoptysis, hemorrhages, or miliary tuberculosis. Hemoptysis and hemorrhages persisting for years in apparently well subjects with no physical signs in the lungs to explain their occurrence have been very puzzling.

Perforation of the trachea and bronchi by caseating glands may cause sudden and progressively severe dyspnea, closely resembling that of diphtheria with cyanosis, unconsciousness, and death. If the obstruction is removed and the patient survives there may be an acute dissemination of tuberculous pneumonic processes throughout the lobe or the entire lung. These sudden manifestations are very apt to occur in apparently well subjects with no suggestions of the approaching danger and no warning until too late.

The pathological changes induced in the lungs by tuberculous bronchial glands are caused by tracheobronchial stenosis and interference with the return circulation of the blood and lymph from the lungs. Pressure upon the trachea and bronchi may force in their walls, narrowing their lumen, causing stenosis. As the chest wall is pulled out this stenosis is relieved, so that the air enters easily enough. As the lung collapses their walls are pushed together again, the stenosis returns, and it is difficult for the air to escape from the lungs. As soon as the interference with the escape of the air causes sufficient accumulation of residual air in the alveoli, expiratory dyspnea develops; as the stenosis increases and the escape of air becomes more difficult, there is the same difficulty and the same consequences that we have in expiratory asthma; if the intra-alveolar distention becomes sufficiently severe the walls of the alveoli will stretch and the terminal areas of the obstructed, occluded bronchi become emphysematous; the larger the bronchus, the greater the terminal areas supplied and the more extensive the emphysema, so that with sufficient obstruction to the trachea or a main bronchus the whole side may become hyperresonant with diminished expansion. If the entering force of the air should be insufficient to force open the lumen of a smaller bronchus, atelectasis of its terminal area results. If the stenosis sufficiently raises the intrabronchial pressure during expiration, the bronchial walls may stretch and cause bronchiectasis, with the characteristic accumulation of purulent fluid not containing tubercle bacilli. The irritation of the bronchi at the point of stenosis, together with the compression of their blood and lymph vessels, causes stasis, with consequent serous effusions, wet rales, and typical bronchitic and pneumonic conditions. Tuberculosis of the bronchial glands may, therefore, cause tracheobronchial stenosis,

with consequent asthmatic, emphysematous, atelectatic, bronchiectatic, bronchitic, and pneumonic conditions in the lungs, which are highly favorable to the growth of tubercle bacilli and the development of tuberculous processes. These conditions are dangerous in themselves, but also dangerous because they are constantly mistaken for primary clinical entities, and the physician is satisfied with the diagnosis of asthma or bronchitis or emphysema, and does not look for tuberculosis of the bronchial glands or lungs. The negative sputum adds to the danger, because it seems to contraindicate tuberculosis.

According to Grancher, the alveolar network of bloodvessels in the lungs holds two liters of blood, and if spread out would cover 150 square meters of surface. Kraemer says: "We have only to remember that all the lymph and blood content of this immense network must pass through the relatively narrow portal of the hilum to realize that slight pressure there might produce enough obstruction to retard the return flow throughout the region of the lung nearest the hilum. Just as enlarged inguinal glands cause edema of the lower extremities and external genitalia, and just as tuberculosis of the cervical glands causes facial edema, so does pressure from enlarged glands within the thorax manifest itself by dilatation of the veins of the face or across the chest or by injuring the recurrent laryngeal, vagus, phrenic, and sympathetic nerves." Just as the mechanical effects of tracheobronchial stenosis predispose to tuberculosis of the lungs by obstructing the escape of air, so the mechanical effects of enlarged glands at the hilum predispose to tuberculosis of the lung by stasis of the lymph and blood currents which is most marked in the region near the hilum, not merely because this region is nearest to the obstruction, but also because the driving force of the collapse of the lung is least felt there. According to von Muralt the force of the collapse of the lung is greatest at the periphery; the greater the distance from the hilum, the greater the force of the circulation; the nearer the hilum, the greater the tendency to sedimentation and depositing ut of tubercle bacilli.

The stasis and slowing of the circulation in the regions of the lung near the hilum predispose to the establishing of tuberculous processes there and make the root of the lung the logical site for the beginning of tuberculous processes in the lung. All cases of tuberculosis of the bronchial glands around the hilum threaten the integrity of the lung. These glands at the hilum are in immediate contact with the lung, and, as Osler says: "It is sometimes difficult to determine in a section through the affected lung where the caseous glands terminate and where the lung tissue begins." Bythell insists that in children pulmonary tuberculosis invariably begins at the roots of the lungs. Quoting Bythell, Leslie says: "Out of 330 successive cases of children examined clinically and radio-

logically he had never seen a single case in which the disease had not obviously originated at the hilus of the lung, nor met one in which the sole or even the primary lesion had been at the apex. Whenever there had been an apical lesion there was in every case revealed by the roentgen-ray a far more advanced lesion at the root of the lung, which had escaped detection by physical examinations, but which was clearly indicated by definite mottling and nodules in the region of the hilus." Bythell regards the glands at the hilum as the actual danger spots and the direct or indirect cause of pulmonary tuberculosis in many cases. Jordan, Cole, Leslie and many others are gradually teaching us that tuberculosis of the apex is secondary to that of the hilum, and has been thought primary because the manifestations are more easily detected there, and also because the apex represents the terminal area of the path through the paravertebral region which tuberculous processes are most apt to follow.

The glands of the hilum are in immediate contact with the lung and the direct extension of tuberculous processes from them into the lung is favored by the associated stasis. The consequences depend upon whether the invaded lung is normal or has been modified by tracheobronchial stenosis. The peribronchitic infiltration of a normal lung has been well described by Jordan. This extension occurs by addition, by aggregation, by sedimentation in the sluggish circulation of the peribronchial tissues of what are more like foreign bodies than aggressive agents; as the tubercle bacilli are deposited out they are encapsulated by connective tissue, there is little or no irritation or hyperemia, the processes are dry, with no exudation; no disintegration of tubercle bacilli, consequently no liberation or absorption of toxins and no syndrome of toxemia. These extensions running along the larger bronchi are purely interstitial and do not affect the mucosa; there is no irritation, consequently no cough, no alteration of breath sounds, and the air content is normal. As the processes reach the smaller bronchi the thickening causes pressure, which may affect the entrance of air into the lumina not well protected by rigid structures, so that suppressed breath sounds over the terminal area of these bronchioles are produced. As soon as the processes reach walls not sufficiently rigid to resist the infiltrations, pressure effects occur. The pathological consequences of peribronchitic infiltrations are not manifested until they reach structures they affect by pressure, and then pain from irritated nerves, collapse of unsupported walls, and atelectatic areas furnish the typical dulness, suppressed breath sounds and the retraction characteristic of fibroid phthisis. This is the gradual fibrosis of the lungs which is not revealed by physical signs until terminal areas are affected. This is the type in which the verdict, "No physical signs in the lungs," therefore no tuberculosis, is so often rendered with such disastrous consequences. Jordan says this is the method of

extension in 50 per cent. of all cases of tuberculosis of the lungs, and that physical signs are not and cannot be present until the terminal areas are reached. This type is dangerous, not only because it may of itself cause death, but also because a multitude of factors may at any time change dry into wet processes, with consequent caseation and softening.

When tuberculous processes extend into a lung which is not normal, but which has been modified by tracheobronchial stenosis or pressure around the hilum, the consequences will depend upon the chief results of the modifications. In one case it may be bronchitic or asthmatic or emphysematous conditions; in another atelectasis. There may be as many different results in the lungs as there are modifying factors producing these results. Wherever the tissues are wet, the foundations for caseous broncholobular pneumonias exist. Wet areas mean caseation with disintegration of lung tissues and tubercle bacilli, the liberation and absorption of toxins, and the syndrome of toxemia.

It has often been asserted that broncholobular pneumonias represent the origin of tuberculous processes in the lungs. That tubercle bacilli are carried to the alveoli by inspiration, and in the alveoli develop and extend from one infundibulum to another until the whole lobule is involved. This racemose or acinous infiltration of lobules is commonly regarded as the type of origin, but it is possible that in some cases the reverse is true, and that extension occurs from the bronchial glands along the peribronchial sheaths to the alveoli, thus causing a lobular infiltration because the lobule is the terminal area of the bronchus. Lobular bronchopneumonias would be the logical result of peribronchial infiltrations into edematous tissues.

The relation of tuberculosis of the bronchial glands to the diagnosis of that of the lungs consists in the recognition of cause and effects. The entrance into and escape from the lungs of air, lymph, and blood are interfered with by the pressure of enlarged bronchial glands upon the air, lymph, and blood-passages. If the lung is dry the effect is chiefly upon the air passages, and we find that not enough air is entering the alveoli to expand them promptly and uniformly. We can hear the slow, uneven, delayed, insufficient expansion of the alveoli, and we know that either there is obstruction to the sufficient entrance of air or that the lobules are tied down in some way so as to restrict their expansion. If the obstruction more especially concerns the escape of air from the lungs then the delayed collapse of the alveoli and prolonged expiration suggest tracheobronchial stenosis. If the pressure upon the air passages is sufficiently great, the breath sounds are more or less suppressed and are louder after coughing when an extra volume of air is forced in. In peribronchitic infiltrations the character of the breath sounds is not so much changed as their volume. Harshness and granular breathing do

not appear until there is roughening of the mucosa. The typical changes in the gradual fibrosis of the lung concern the interstitial tissues chiefly and do not cause dulness until atelectasis develops. Suppression of breath sounds and insufficient, irregular expansion of the alveoli are the landmarks of peribronchitic infiltrations as they thread their way through a dry lung. Pain in the terminal areas is often characteristic, and is probably caused by pressure upon the accompanying nerves.

When the return circulation of blood and lymph from the lung is obstructed and the lung is subjected to the backward pressure and danger of edematous infiltrations, the physical signs are those of wet conditions. It is much easier to detect these evident changes, and they are much more pronounced, but they are sometimes mistaken for other conditions. Chronic bronchitis, asthma, and emphysema often cloak tuberculous processes, and acute infections for a time often reveal them; but as the acute hyperemia disappears and the wet sounds dry up we fail to see the connection between existing peribronchitic infiltrations and transient physical signs. We ascribe to grippe, typhoid, measles, and colds the power to initiate tuberculous processes in the lung, but it is possible that they reveal the existence of these processes.

The treatment of tuberculosis of the lungs is influenced by the knowledge that there is an etiological relationship with that of the bronchial glands, because these glands must first be healed before the chancre of perpetual reinfection is removed. This emphasizes the necessity for time. Long after the physical signs in the lungs have become favorable, just as it was long before they were manifested, the sore spots in the bronchial glands remain dangerous and difficult to control. It is possible that the persistency of these sources of infection explains the relapses and the failures to maintain recovery in many cases. The diagnosis and treatment of tuberculosis of the lungs may begin and end in that of the bronchial glands.

A CASE OF DIABETES INSIPIDUS WITH A PECULIAR NECROPSY FINDING IN THE POSTERIOR LOBE OF THE PITUITARY BODY.

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Various changes have been described in the pituitary gland and its neighborhood, at the base of the brain, as having been discovered at postmortem examinations on cases of diabetes insipidus.

J. Camus and G. Roussy[1] are among those who have experimented on the subject. About eighteen dogs were operated on and various areas at the base of the brain in the immediate neighborhood of the pituitary gland were destroyed, and in some animals the pituitary gland itself was destroyed. By these experiments it was proved that polyuria may result even when the lesion is not limited to the pituitary gland. In five cases polyuria resulted, though the experimental puncture did not touch the pituitary gland. The infundibulum seems to be of special importance, and one observation showed that if the infundibulum were preserved it was possible for the pituitary gland itself to be removed without polyuria resulting.

By some authors the "pars intermedia" of the pituitary body has been specially incriminated.[2] Ependymitis, or tumor of the floor of the fourth ventricle, has occasionally been accompanied by diabetes insipidus,[3] and Claude Bernard, as is well known, was able to experimentally produce simple polyuria in animals by puncture of the floor of the fourth ventricle at a point a little above his so-called "glycosuric centre."

The relations between the pituitary gland and diabetes insipidus have recently been dealt with by C. Römer,[4] M. Simmonds,[5] Harvey Cushing,[6] P. Fleurot,[7] D. B. Jewett,[8] Erich Meyer[9] and others; and the allied subject of the effect of metastatic tumors of the pituitary gland has been discussed by Simmonds[10] and S. Erdheim,[11] the latter demonstrating the case of a woman with "Simmonds's syndrome" (the association of mammary carcinoma with polyuria, due to cancerous metastasis in the pituitary gland). Many papers have also been published more or less bearing on the relations of the pituitary gland to imperfect sexual development and infantilism as well as to diabetes insipidus.[12]

[1] Comptes rendus de la Société de biologie, Paris, 1914, lxxvi, 773 and 877; see also Camus and Roussy, Diabète Insipide et Polyurie dite Hypophysaire, Presse médicale, Paris, 1914, xxiii, 517.

[2] Cf. E. Frank, Ueber Beziehungen der Hypophyse zum Diabetes insipidus, Berl. klin. Wchnschr., 1912, xlix, 393.

[3] K. Pichler, Zentralbl. f. inn. Med., Leipzig, 1903, xxiv, 745. Pichler gives references to similar cases in the literature. Cf. the old experiments of Claude Bernard on the Experimental Production in Animals of Glycosuria and Simple Polyuria.

[4] Deutsch. med. Wchnschr., 1914, xl, 108; and C. Römer, München. med. Wchnschr., 1913, lx, 2755 (Aerztlicher Verein in Hamburg, November 25, 1913).

[5] München. med. Wchnschr., 1913, lx, 127.

[6] The Pituitary Body and its Disorders, 1912, pp. 17, 267.

[7] Thèse de Doctorat, Paris, 1914.

[8] Med. Record, New York, 1914, lxxxv, 242.

[9] Berl. klin. Wchnschr., 1912, xlix, 1642 (unterelsässicher Aerztev., June 29, 1912).

[10] München. med. Wchnschr., 1914, lxi, 180.

[11] K. k. Gesellschaft der Aertze in Wien, May 29, 1914, Wien. klin. Wchnschr., 1914, xxvii, 867.

[12] See Erich Ebstein, Ueber Eunuchoidismus bei Diabetes insipidus (with many references to previous literature), Mitt. a. d. Greuzgeb. d. Med. u. Chir., 1913, xxv, 441. A. von Strümpell, Med. Gesellsch. zu Leipzig, January 20, 1914; München. med. Wchnschr., 1914, lxi, 504. Pierre Marie and Boutier, Société de Neurologie, Paris, April 3, 1913 (Rev. neurol., Paris, 1913, xxi, 555); F. P. Weber, Brit. Jour. Child. Dis., 1912, ix, 211; T. R. Whipham, Proc. Roy. Soc. Med. (London), Section for Diseases of Children, 1915, viii, 10; Sprinzels, Wien. klin. Wchnschr., 1912, xxv, 937 (K. k. Gesellsch. der Aerzte in Wien, June 7, 1912).

In many cases of diabetes insipidus, symptoms have been observed during life pointing to the presence of lesions at the base of the brain. Clinically a connection between diabetes insipidus and congenital or acquired syphilis has often been suspected; in some cases the belief in such a connection has, I think, received confirmation *ex juvantibus*, that is to say, from satisfactory results of antisyphilitic treatment. In several other cases a connection of some kind with tuberculosis seems to have existed.

Our present case is that of a tuberculous man who suddenly developed diabetes insipidus about two years before his death, which was due to pulmonary and laryngeal tuberculosis. At the necropsy a peculiar change in the posterior lobe of the pituitary body was found.

Case History. The patient, F. A., aged thirty-seven years, was admitted to the hospital on March 31, 1915, and died on June 21. He was a thin man, weighing 115 English pounds on admission, and said he had lost nine pounds in weight during the previous nineteen days. His polyuria had apparently commenced suddenly in August, 1913, after a slight operation on his neck, probably the removal of an enlarged lymphatic gland from the right side. This operation did not prevent him making a long railway journey on the same evening, but he commenced to experience great thirst (polydipsia) immediately afterward, and since then he had continuously suffered from polydipsia and polyuria. During the last two months he had had a cough and anorexia, and for one month he had been expectorating mucopurulent sputum.

In the hospital he presented the physical signs of pulmonary and laryngeal tuberculosis, had a hectic type of fever, and steadily lost ground. His mucopurulent sputum swarmed with tubercle bacilli. His urine, which was of about the same specific gravity as ordinary tap-water, pale, clear, and free from albumin and sugar, averaged about 10 liters in the twenty-four hours, sometimes more, sometimes less. On one occasion the daily quantity was as much as 13,250 c.c. His blood serum gave a negative Wassermann reaction for syphilis. His brachial systolic blood-pressure varied between 90 and 115 mm. Hg. His pupils were equal and reacted properly to light and accommodation. Ophthalmoscopic examination showed nothing abnormal. There was no hemianopsia; the visual fields (both for white and for colors) and visual acuity were normal (Dr. C. Markus). Roentgen-ray photographs of the base of the patient's skull (taken by Dr. James Metcalfe) seemed to show that there was no enlargement of the pituitary fossa. During the last days before the patient's death (June 21, 1915) the average amount of urine was less, namely, about 6000 c.c. in the twenty-four hours.

Necropsy and Microscopic Examination. Both lungs were "stuffed with" miliary tubercles; there were no cavities. There was tuberculous laryngitis (macroscopic and microscopic examina-

tion). The heart, pericardium, and aorta showed nothing special. The liver was not enlarged, but looked somewhat fatty. The spleen was slightly enlarged, measuring 12 x 8 x 4 cm., but otherwise by macroscopic and microscopic examination it appeared normal. The kidneys, suprarenal glands, and thyroid glands likewise appeared normal (microscopic as well as macroscopic examination). Nothing special was observed in the pancreas, alimentary canal, or in the

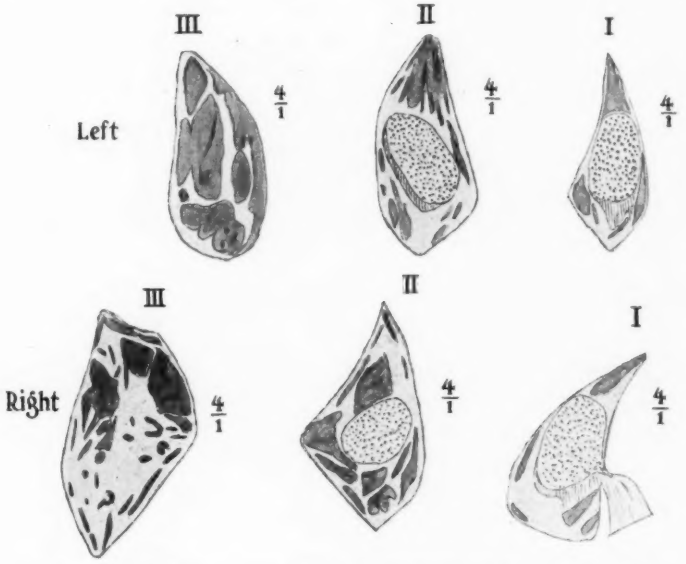

FIG. 1.—A series of six sections of the pituitary body cut parallel to each other, on a vertical-sagittal plane. They are represented diagrammatically four times their natural size. The three in the upper row were cut to the left of the middle line and the three in the lower row were cut to the right of the middle line. The pair marked *I* are those nearest the middle line; the pair marked *III* are those farthest from the middle line; while the pair marked *II* were cut on a plane between *I* and *II*. In these sections the dotted portions represent the anterior lobe (pars glandularis), while the rest represents the posterior lobe (pars nervosa). The two lateral sections (*III*) consist exclusively of posterior lobe substance, while in *I* and *II* the anterior lobe substance is almost completely surrounded by posterior lobe substance. The dark portions in the posterior lobe substance are areas of the yellowish-brownish lipoid cells. (See Figs. 2 and 3.)

testis or epididymis on either side. There were some enlarged lymphatic glands in the neck. The bone marrow of the head and upper part of the shaft of the left humerus was examined macroscopically and looked as if it had not undergone much hemopoietic reaction. The spinal cord was not examined, and in the examination of the brain nothing abnormal was observed excepting with regard to the pituitary body.

The Pituitary Body. At the necropsy the pituitary fossa was found to be not much if at all enlarged, but the posterior lobe of the pituitary body appeared abnormal, and the whole region was removed for further examination. Several sections of the pituitary body were cut; all of them were cut parallel to each other, on a vertical sagittal plane. There could be no doubt whatever that the posterior lobe (pars nervosa) was relatively enlarged in proportion to the anterior lobe (pars glandularis). The posterior lobe almost completely enclosed the anterior lobe, and was of a yellowish-brownish color, the color appearing to spread right into the posterior wall of the pituitary fossa. Fig. 1 represents diagrammatically six of the sections under low magnification (four times the natural size).

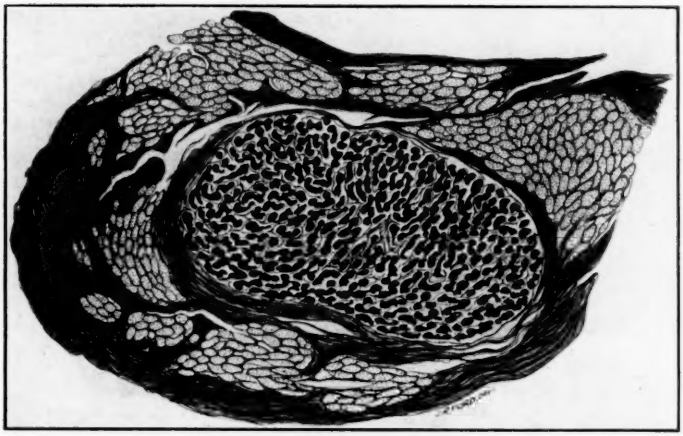

FIG. 2.—A drawing of a section of the pituitary body (magnified 15 times) similar to *II* in the lower row of Fig. 1. The substance of the anterior lobe, which has the normal glandular structure, is almost completely surrounded by posterior lobe substance, which is remarkable for containing large clumps of granular cells.

The three in the upper row were cut to the left of the middle line and the three in the lower row were cut to the right of the middle line. The pair marked *I* are those nearest (to the left and right respectively of) the middle line. The pair marked *III* are those farthest from the middle line, while the pair marked *II* were cut on a plane between *I* and *III*. In these sections the dotted portions represent the anterior lobe (pars glandularis) while the rest represents the posterior lobe (pars nervosa), which in *I* and *II* is seen to almost completely surround the anterior lobe. The two lateral sections (*III*) consist exclusively of posterior lobe substance. The dark portions in the posterior lobe are areas of the yellowish-brownish substance which has given the posterior lobe its decided color.

Fig. 2 is a drawing of a section similar to *II* in the lower row of

Fig. 1, but under considerably higher magnification (magnified 15 times). The substance of the anterior lobe is seen to present the normal glandular structure, but the posterior lobe, which almost completely surrounds it, is remarkable for containing large clumps of granular cells. Part of one of these clumps (from a section stained with Sudan III), magnified 300 times, is represented in Fig. 3, so as to further illustrate the nature of the cells in question. They are rather large cells with small nuclei, which stain deeply with hematoxylin. Their cytoplasm has a granular appearance and many of them take on the Sudan III coloration very well, and show that the granules are really minute droplets of a lipoid substance. In others

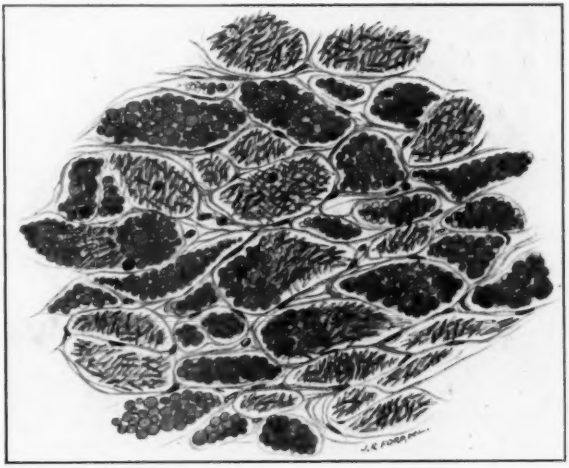

FIG. 3.—A drawing from one of the clumps (see Fig. 2) of cells in the posterior lobe substance of the pituitary body (magnified 300 times). The cytoplasm of some of these cells is full of minute lipoid droplets which have taken on the Sudan III stain very well. The cytoplasm of others of the cells is rich in fatty acid crystals and has taken on the Sudan III stain relatively badly.

of these cells, which stain less well with Sudan III, the cytoplasm appears to be full of minute crystals, doubtless fatty acid crystals of some kind; and probably it was a transformation of the lipoid droplets into fatty acid crystals that caused these cells to take on the Sudan III stain relatively badly.

We think that these cells, which are possibly of neuroglial origin, may be regarded as one kind of "compound granular cells" (Körnchenzellen), the presence of which in considerable numbers forms a feature in various abnormal conditions of the central nervous system. Doubtless the lipoid-containing cells in question gave the posterior lobe substance of the pituitary body in the present case its decided yellowish-brownish pigmentation, which reminded one

of the color of the cortex of suprarenal glands and of some tumors of suprarenal cortical origin.

Many changes in the pituitary body and the base of the brain have (as we pointed out at the commencement of this paper) been described in cases of diabetes insipidus, but we are not aware that an exactly similar change to the one observed in our present case has as yet been recorded. It is impossible to avoid the conclusion that the changes in the pituitary body in the present case were in some way the result of the patient's tuberculosis.

In conclusion, we have to thank Mr. S. G. Shattock, Dr. J. C. G. Ledingham, and Dr. Kinnier Wilson for very kindly helping us in the examination of the sections.

NOTE.—In producing the three figures the original drawings have been considerably reduced, Figs. 2 and 3 by one-quarter and Fig. 1 by two-fifths. The printed descriptions are therefore no longer correct in regard to the question of magnification.

REVIEWS

FRACTURES AND DISLOCATIONS. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Associate in Surgery, Northwestern University Medical School; Associate Surgeon, Mercy Hospital; Attending Surgeon, Cook County Hospital, Chicago, Ill. Pp. 888; 656 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

IN the preparation of his book the author has used material from his own experience and culled other information from the literature on the subject. He contends, and wisely, that intelligent treatment of fractures and dislocations must be based on a proper conception of the pathology involved. A clear conception of the nature of the bony injury in fractures is essential and this can be had only with the aid of sufficiently numerous roentgen-ray views. These views the author has interpreted in his book by making careful line drawings of the fractures, thus obviating the possible misinterpretation so common in the reading of a fracture plate. He does not, however, lay enough stress upon the necessity of having two views of every fracture. Such illustrations are noticeably lacking especially in the fractures of the upper half of the femur. It is well known that an antero-posterior view shows frequently good position when a lateral view will show no approximation at all.

The chapter on the operative treatment of fractures is very interesting, instructive and up to date. The author here states that bone work is best done by experienced surgeons in this line and that strict asepsis must be observed. Perfectly true, but such surgeons are made by experience which, unfortunately, must be gained.

The use of the Steinmann nail extension is spoken of and advocated as the best in many fractures needing extension. The writer should, however, describe the removal of a modern Steinmann nail which unscrews in its middle thus allowing half to be pulled out each side and not necessitating pulling an exposed, supposedly dirty end through the tissues and bone.

The treatment by external fixation is well and thoroughly described but could be improved by more detail as regard the dressings and splints. More illustrations of the completed final dressing would be a great addition, for in reality after the reduction this is the important feature in all fracture treatment. There are many splints, plaster moulds and methods of fixation and traction generally

unknown that could well be incorporated in this excellent work, preferably presented as illustrations.

The book is thoroughly well written and edited and is unusually free from typographical errors. It covers the subject completely, and is a treatise that any physician or surgeon should have at his command. E. L. E.

VENEREAL DISEASES. A MANUAL FOR STUDENTS AND PRACTITIONERS. By JAMES R. HAYDEN, M.D., F.A.C.S., Professor of Urology in the College of Physicians and Surgeons, Columbia University, New York. Fourth edition. Pp. 365; 133 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

THE fact that this work of Hayden's on venereal diseases has already passed through three editions is sufficient testimonial as to its merit and popularity. This new edition has been thoroughly revised and enlarged and the subject matter brought up to date with the addition of numerous new illustrations.

Dr. Hayden has covered the subject in a notably clear and concise manner, and it is obvious that his presentation is the expression of personal experience. Of the thirty-six chapters, eighteen are devoted to syphilis, nine to gonorrhea, and nine to other forms of venereal disease.

It occurs to the critic that insufficient and disproportionate space is given to seminal vesiculitis as compared with prostatitis; also that the author is incredulous of the value of epididymotomy, at least that the indications and contra-indications are not satisfactorily drawn.

Many will disagree with Hayden relative to the treatment of acute posterior urethritis by injections and irrigations by using a catheter. Again, in view of the generally acknowledged utility of sera and bacterins especially in gonorrheal arthritis, more stress might be laid on therapy by these agents, including a statement of the technic of their administration.

We do not agree that excision of the chancre, when practicable, is of no value, and that so soon as the initial lesion of syphilis appears the entire system is infected to maximum degree. Contrary to the majority opinion, the author apparently places mercury as the sheet anchor in the treatment of syphilis, as the description of its administration precedes that of salvarsan or neosalvarsan. We would also take exception to the statement that it is "not worth while to test the complement fixation reaction until after the end of the second year" of antisyphilitic treatment.

Considered in its entirety, this book is most admirable, and is the most practical treatise on venereal diseases extant for the use and guidance of general practitioners and students. B. A. T.

A Text-book of Practical Gynecology. By D. Tod Gilliam, M.D., Emeritus Professor of Gynecology in Ohio State University College of Medicine, and Earl M. Gilliam, M.D., Professor of Diseases of Women in the Ohio State University. Fifth revised edition. Pp. 681; 366 illustrations. Philadelphia: F. A. Davis Company, 1916.

The mere fact that this book is now in its fifth edition should be *prima facie* evidence that it has merits and is extensively used. There are one or two features of the book, however, which must bear criticism. It is surprising to note, in spite of the fact that the book is just off the press, that the subject of radium and roentgen-therapy is not even mentioned. The general arrangement of the book shows carelessness, as for example the interposition of a chapter on upper abdominal surgery between two chapters on ovarian conditions. The illustrations might have answered for the first edition of this work, but we certainly expect something better than crude drawings at this late date. The chapter on the urinary organs is antiquated and is badly in need of revision. In short, this text-book in its present state, cannot be favorably compared with the more recent contributions to the subject. F. E. K.

Manual of Otology. By Charles Edwin Perkins, M.D., F.A.C.S., Professor of Clinical Otology in New York University and Bellevue Hospital Medical College. Pp. 445; 120 engravings. Philadelphia and New York: Lea & Febiger, 1916.

For a text-book for students and practitioners, as this *Manual* professes to be, it is one of the most concise, lucid, and thorough that the reviewer has seen, and it might with propriety and profit be studied by the fairly advanced specialist as well, as it gives accurate scientific information concerning all of the more common, and most of the rare diseases of the ear. Especially to be commended, from the stand-point of the student, are the early chapters on anatomy, physiology, and methods of examination, in which the subjects are treated in a manner different from the somewhat stereotyped form of most manuals, and with an originality in text and illustration that makes an intricate study both clear and interesting. While the work shows largely the results of the author's personal experience, there is a commendable absence of case histories, which have always seemed to the reviewer to be out of place in a work of limited size and scope.

One of the most interesting and instructive features of the book, perhaps, is the space devoted to diseases of the internal ear, particularly of the vestibular portion, for, through the recent researches

of well-known workers, the part this organ plays in modern medical diagnosis is rapidly becoming prominent, and it is a necessity for anyone professing to do ear work to at least understand the fundamental laws governing the spontaneous and induced vestibular reactions, their relations to other parts of the body, and their value in differential diagnosis. Very wisely, however, the author has not gone into the fascinating realm of cerebellar localization, which abstruse subject is eminently out of place in a work of this character.

Dr. Perkins' descriptions and illustrations of operative procedures are all that could be desired, and the reader is not burdened with several different methods of operating, where one standardized one will suffice.

Many of the excellent illustrations with which the book abounds are from photographs; others are well planned schematic representations, and the accompanying explanatory text is very clear. All are original. Altogether it is a complete and practical text-book, full of interest and instruction for anyone. G. M. C.

CARE AND FEEDING OF INFANTS AND CHILDREN. By WALTER REEVE RAMSEY, M.D., Associate Professor of Diseases of Children, University of Minnesota. Pp. 290; 123 illustrations. Philadelphia: J. B. Lippincott Company, 1916.

THIS book is written for nurses. A nurse who studied and retained the information contained between its covers would not only be better informed than most of her profession, but would be quite sure to know more about babies and children than most physicians. In other words the book is well written and thorough. The chapters are logically arranged, and good judgment is used in not making certain ones too intricate. The illustrations convey what they should very clearly, and are well selected. A. G. M.

MEDICAL AND SURGICAL REPORTS OF THE EPISCOPAL HOSPITAL. Edited by ASTLEY P. C. ASHHURST, M.D. Volume III. Pp. 352; 126 illustrations. Philadelphia: Wm. J. Dornan, 1915.

THE third volume of the *Reports of the Medical and Surgical Staff of the Episcopal Hospital* is a splendidly constructed and admirably edited example of what a hospital report should be. A hospital report of this type is meant primarily to put on record the work that is done in the hospital and to report cases of an unusual type which are worthy of record, but which, for various reasons,

would not be placed in current medical periodicals. This is what has been accomplished in the present volume. Methods of diagnosis and results of treatment as practised in the Episcopal Hospital are reported as well as numerous unusual cases. The great majority of these would probably not see the light of cold print were it not for the hospital report, and thereby there would be a loss to the medical world.

The editor of this volume is certainly deserving of much praise. Probably without his energetic efforts it would have been impossible to have secured so many admirable contributions; it is certainly through his efforts that such a first-class and complete publication has been achieved. J. H. M., Jr.

THE BASIS OF SYMPTOMS. THE PRINCIPLES OF CLINICAL PATHOLOGY. By Dr. LUDOLPH KREHL, Ordinary Professor and Director of the Medical Clinic in Heidelberg. Translated from the seventh German edition by A. F. BEIFELD, Instructor in Medicine, Northwestern Medical School, with an introduction by A. W. HEWLETT, Professor of Internal Medicine, University of Michigan, Ann Arbor. Pp. 517. Philadelphia and London: J. B. Lippincott Company.

AFTER an interval of nine years, Hewlett's well-known translation of Krehl's *Clinical Pathology* now appears in a third English translation by Beifeld under the new title of *The Basis of Symptoms*. The translator states that the change was made in order to emphasize the immediate relation of the contents to clinical medicine. Nevertheless, in view of the popularity of the former editions and the close adherence of the present to the former texts, the advantage of such a change of titles is at least questionable. In other particulars, however, the translator's service is excellent. In many instances his parenthetical additions alone save the treatment of a given topic from being inadequate and antiquated, and it is only a pity that more care was not observed in placing the German text in better harmony with the translator's more modern view-point. Examples of such valuable inserts can be found in the discussions on the origin of the heart beat (pages 53 and 54), paroxysmal tachycardia (pages 57 and 58), auricular fibrillation (pages 65 and 66), Fischer's theory of edema (page 93), the cytodiagnosis of exudates (page 94), the relation of the hypophysis to adiposity (page 318).

The twelve chapters treat of (1) the circulation; (2) the blood; (3) infection and immunity; (4) respiration; (5) digestion; (6) nutrition and metabolism; (7) disturbances of carbohydrate mechanism; (8) metabolism of the purin bodies; (9) constitutional diseases and diatheses; (10) fever; (11) secretion of urine; (12) nervous system. One regrets the absence of discussion of such topics as

auricular flutter, venous blood-pressure, blood-platelets in hemorrhagic diseases, acidosis factors in dyspnea and kindred subjects. The references which were formerly at the bottom of each page have been much extended and collected at the end of each chapter. The great preponderance of German citations to the neglect of English-speaking authorities is unfortunate, though hardly unexpected. A case in point is found in the relationship of the islands of Langerhans to diabetes, where Weichselbaum is quoted and Opie's work omitted. The illustrations of the former editions have been removed, so that this edition only contains twelve more pages than does the second.

As the earlier editions of this book do not appear to have been reviewed in this JOURNAL, a few remarks on the nature of the work will perhaps not be considered out of place. As both of its English titles imply, it is an attempt to "interpret the various pictures observed in the clinic from the stand-point of disturbed physiology" and "to foster a more definite leaning (by the clinician) upon the biological sciences in general." Perusal of any one of the twelve chapters will undeniably foster these admirable principles; but it is also true that the various branches of this important and far-reaching subject can in 520 pages necessarily only be touched upon in a cursory if not superficial manner. He would, indeed, be doomed to disappointment who felt that after reading the chapter on the circulation, for instance, he had really covered all the disturbances in function of this extensive system. As a text-book, then, of an important branch of medicine, or as a valuable repository of pathologico-physiological facts, the book leaves much to be desired; as a correlation of a certain number of clinical symptoms with their pathological causes and as a stimulus to the "functional outlook on disease," it should be a valuable reminder to many practitioners and a pleasant review to a still wider circle. E. B. K.

DISEASES OF OCCUPATION AND VOCATIONAL HYGIENE. Edited by GEORGE M. KOBER, M.D., LL.D., Professor of Hygiene, Georgetown University, Washington, D. C.; President of the Section on Hygiene of Occupations, XV International Congress on Hygiene and Demography; Chairman of the Section on Industrial Hygiene of the American Public Health Association (1915); Secretary of the Association of American Physicians, and WILLIAM C. HANSON, M.D., formerly with the Massachusetts State Board of Health. Pp. 918; 42 figures. Philadelphia: P. Blakiston's Son & Co., 1916.

IT was inevitable, in view of the recent awakening in this country to the importance of vocational diseases and hygiene, that a comprehensive text-book upon the subject should appear. Until very

recently, however, this has been impossible on account of the paucity of American statistical data. The publications of the *Transactions of the XV International Congress on Hygiene and Demography*, of the latest mortality statistics by the United States Census Bureau, and of industrial insurance statistics by the Metropolitan Insurance Company as well as of numerous monographs upon special investigations have greatly improved this situation. Consequently, it has been possible for Kober and Hanson to give us in this volume the most complete and authoritative presentation of the subject yet submitted to the English-speaking public.

It is really three books in one. The first one, designated Part I, is in itself a system of the diseases of occupation. The occupational intoxications are discussed by such authorities as Thomas M. Legge, Emery R. Hayhurst, George L. Apfelbach, Sir Thomas Oliver, Harry Linenthal, Alice Hamilton, Louis Casamajor, and Ludwig Teleky, *privat dozent* for social medicine at the University of Vienna. Anthrax and the relation of parasites to occupation are described by Langdon Frothingham and Bailey K. Ashford respectively. Compressed-air illness is presented by Seward Erdman, whose name is identified with the investigation of those cases which occurred during the construction of the East River tunnels in New York. The final one of the specific occupational diseases, that of diminished atmosphere, especially as seen in aviators, is most interestingly presented by the senior editor.

The systemic occupational diseases, including the dust diseases of the lungs and diseases of the blood, circulatory system, and kidneys are covered by Sir Thomas Oliver and Thomas S. Lee. One of the most scientific and valuable chapters in the entire volume is that upon fatigue and occupation, by Fredric S. Lee, who is the recognized leader in this line of research in this country. Chapters upon occupational affections of the nose, mouth, throat, eye, ear, and skin are presented by specialists in the particular fields of study. Oliver closes this section of the book with a discussion of electrical injuries and electrical shock.

Part II, 347 pages, deals with the etiology and prophylaxis of occupational diseases in general and with vocational hygiene as related to the processes which are injurious to health. It is contributed almost entirely by Dr. Kober, and will be of interest to employers, employees, public health officials, and indeed all those interested in the prevention of occupational hazards. There is also included in this part of the book the list of industrial poisons which was edited by the permanent advisory council of hygiene of the International Association for Labor Legislation. It covers 54 poisons, giving for each the branches of industry in which the poisoning occurs, the mode of entrance into the body, and the symptoms of poisoning. There are other valuable tables in this section.

Part III has to do with the relation of clinics, statistics, govern-

mental study, and legislation to occupational diseases. Among its most interesting chapters are those of Luigi Devoto, professor and director of the Milan Clinic, the first clinic established for occupational diseases, upon the purposes and accomplishments of that clinic, and of Frederic L. Hoffman upon the mortality from tuberculosis in dusty trades. A chapter by George C. Whipple, of the Massachusetts Institute of Technology, upon the uses and fallacies of statistics will be appreciated by all who are not familiar with the technical difficulties of statistical data. This part of the book is planned to be of special help to those called upon to investigate the relations of occupation to disease. T. G. M.

MEDICAL CLINICS OF CHICAGO. Vol. II, Nos. 1 and 2. Philadelphia and London: W. B. Saunders Company, 1916.

The Medical Clinics of Chicago have now completed their first year of active publication and are starting out on the second, apparently with no decrease in vigor and considerable improvement in general character. The first number of the new volume contains several important and interesting clinics, and likewise one or two which might have well been omitted. Comparisons are odious, but it would be unfair not to mention certain contributions in this number: Dr. Brophy gives a splendid medicodental discussion on Oral Infection, Dr. Abt discusses most completely the Feeding of the Normal Baby, and Dr. Edwards gives a well-prepared lecture on the Use of Digitalis.

The second number of the second volume is likewise interesting and instructive. Dr. Portis has a very interesting but rather incomplete clinic on Syphilis of the Stomach. Dr. Abt's article can be again selected for special commendation, as well as that of Dr. Biefeld.

Taking everything into consideration it can be said that the clinics are showing a healthy improvement, but there are still criticisms which may be made and which have been made, and which still hold good, but, on the whole, they present a novel method of giving to a larger class of physicians a most valuable course in clinical medicine. J. H. M., JR.

PROGRESS
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UNDER THE CHARGE OF

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The Vaccine Treatment of Asthma, in Bengal.—L. ROGERS (*Practitioner*, 1916, xcvi, 573) reports a series of 13 cases of bronchial asthma treated with autogenous vaccine. Cultures were made on glycerin-agar tubes from freshly obtained sputum, two tubes being inoculated from a single loopful, and about six tubes used in each examination to ensure some of the colonies being well separated. On the following day, subcultures were made from the fine pneumococcal and streptococcal-like colonies, a number of them being taken up so as to get as many strains as possible in the tubes used for making the vaccine. Occasionally the culture consisted so purely of fine colonies that the vaccine could be prepared from the primary culture, but this was exceptional. If the subculture was a thin one, it was smeared over the surface with a platinum loop and reincubated until a uniform thin layer of growth was obtained. Five cubic centimeters of sterile salt solution were added to each tube, which was then heated to from 56° to 60° for one hour; 0.5 per cent. of carbolic acid was added, and after mixing well the fluid was put up in doses of 0.5 and 1 c.c. The first dose was 0.5 c.c., which usually contained about 50,000,000 organisms. If no febrile, but only a slight local reaction occurred, a dose of 1 c.c. was given in five days and repeated weekly. Occasionally it was necessary to increase the dose to 2 c.c. The organisms present varied considerably in different cases, while some of the vaccines were mixed cultures of more than one variety of coccus. Most frequently diplococci were found in the largest numbers and sometimes nearly in pure culture. They were nearly always Gram-positive and sometimes capsulated. Streptococci were also commonly present, and were sometimes the predominating organisms. The cultural characteristics of

the organisms were not studied for lack of time. Cures are reported in a number of instances, the largest being of two and a half years' duration. All but two of the patients showed decided benefit, and in these the treatment was discontinued before it could be given a fair trial.

The Etiology of Epidemic Poliomyelitis.—E. C. ROSENOW, E. B. TOWNE and G. W. WHEELER (*Jour. Am. Med. Assn.*, 1916, lxvii, 1202) report results of their recent investigations of epidemic poliomyelitis in a preliminary note. They have made a bacteriological study of throats, tonsils, blood, spinal fluid, the central nervous system, and other tissues in cases of acute poliomyelitis in the present epidemic both in Rochester, Minn., and in New York City, with particular reference to the infecting power of the bacteria isolated. They isolated a peculiar polymorphous streptococcus, often in large numbers, from the throat, from material expressed from tonsils, and from abscesses in tonsils of a large series of cases of epidemic poliomyelitis. They also obtained similar organisms from the ventricular fluid after death and from blood during life in one instance but not from the spinal fluid. In twelve consecutive cases of poliomyelitis which came to autopsy in New York, they obtained this same organism from the brain and cord and from the intervertebral ganglia and lymph nodes in some of the cases. This confirmed the results of Mathers in his studies of the brain and cord. The polymorphous streptococcus produces on aërobic blood-agar plates fine, dry, non-adherent, slightly green colonies which may show a hazy zone of hemolysis after forty-eight hours. The cultural characteristics vary with the conditions of artificial growth employed. Involution forms may occur. One of the striking characteristics of this organism appears to be the fact that with changes in its artificial medium it becomes transformed from a relatively large coccus to an extremely minute organism resembling the globoid bodies described by Flexner and Noguchi. After filtration of cultures through Berkefeld N filters a growth can be obtained from the filtrate, and in suitable medium, the large forms may be obtained from this material which originally contained only the small globoid bodies. Paralysis with lesions in the central nervous system has been produced in guinea-pigs, rabbits, dogs, cats, and monkeys by intravenous or intracerebral injection, with this peculiar streptococcus from practically all of the 52 cases of acute poliomyelitis. Furthermore, it has been produced by injecting the emulsions of pus expressed from tonsils, emulsions of extirpated tonsils and emulsions of the brain. It has also followed injection of the primary mixed culture containing chiefly the peculiar streptococcus, and by injection of the pure cultures from throats, from material expressed from tonsils, and from the abscesses in tonsils removed from living patients and necropsy cases. Similar results have been secured from cultures obtained from the brain and cord.

Lead Poisoning from Projectiles Retained in the Body.—M. LOEPER and G. VERPY (*Progrès méd.*, 1916, xl, 81) report studies on 16 patients carrying old lead projectiles embedded in their tissues. The authors had observed symptoms which they found difficult to explain, *i. e.*, hypertension, albuminuria and cylindruria, constipation

and colic, and anemia. Suspecting that the patients might be suffering with a latent saturnism, they made chemical examinations of their urines, and in six of the sixteen they demonstrated the presence of lead. The lead was found to the amount of 0.5 to 1 mg. per liter of urine, or an excretion of more than 1 mg. daily. The intestinal and nervous symptoms they could not relieve, but in three cases the albuminuria (0.5, 0.75, and 3. gm. per liter respectively) disappeared completely within two to three weeks after removal of the lead bullet, and lead could no longer be found in the urine. Likewise, they had under observation two patients with anemia (2,800,000 and 3,200,000 red blood cells respectively) in whose erythrocytes basophilic granulation was observed. These patients were also benefited by extraction of lead bullets. The authors believe, therefore, that lead bullets or bits of shrapnel, which are not causing trouble locally, may, nevertheless, be responsible in some cases for toxic effects whose nature should be suspected.

Experimental Studies in the Etiology of Acute Epidemic Poliomyelitis.—J. W. NUZUM and M. HERZOG (*Jour. Am. Med. Assn.*, 1916, lxvii, 1205) report bacteriological studies of the recent epidemic of acute poliomyelitis in Chicago. All of their material was obtained from the Cook County Hospital. They have obtained a Gram-positive micrococcus from the tissues of the central nervous system, tonsils, mesenteric lymph glands, and from the cerebrospinal fluid obtained during life. Cultures of this organism, when injected in monkeys, produced the typical clinical and pathological picture of acute poliomyelitis. Definite flaccid paralysis has been produced in dogs and in many young rabbits. The organism grows better aërobically than anaërobically. Anaërobic cultures in fluid mediums were passed through Berkefeld filters V, and inoculations of the filtrate into suitable mediums produced a growth of the larger form of the organism seen in aërobic cultures. In the tissues from the central nervous system of poliomyelitic material preserved in 50 per cent. sterile glycerin, this same micrococcus was alive after a period of thirty-five days, and could be cultivated in pure culture on suitable mediums.

SURGERY

UNDER THE CHARGE OF

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The Surgical Treatment of Perforated Ulcer of the Stomach.—WILENSKY (*Ann. Surg.*, 1916, lxiv, 403), says that the ideal method of operative treatment would comprise the closure of the perforation plus some procedure for the cure of the underlying ulceration. The

feasibility of doing anything further than a purely life-saving measure is determined by the general condition of the patient at the time of the operation and by the extent and degree of the associated peritonitis. Nineteen cases were operated on for this condition. All were between twenty-five and forty-five years of age. Nine died (47 per cent.). The absolute indications for the addition of gastro-enterostomy to the closure of the perforation at the primary operation are given as follows: (1) Stenosis of the pylorus or duodenum, which may result from old or recent peripyloric or periduodenal adhesions. (2) To safeguard the stitches. (3) When the perforation is only packed or drained, gastro-enterostomy, with unilateral exclusion of the area of perforation, is the only safe way of preventing the formation of a duodenal fistula. The development of such a condition (and if nothing is done for its prevention it will almost invariably develop) is a most serious end, in the great majority of the cases, a fatal lesion. Gastro-enterostomy also offers the following advantages: (1) It facilitates the early nutrition of the patient. (2) It exerts a favorable influence upon the underlying ulcerated condition. (3) It diminishes the danger of subsequent hemorrhage or perforation in coexisting ulcers and favors the healing. The following objections have been made to the addition of a gastro-enterostomy at the primary operation: (1) It prolongs the operation and adds to the shock. (2) It spreads infection to uninvolved portions of the general peritoneal cavity and into the lesser peritoneal sac. (3) Gastro-enterostomy is not necessary because, in the first place, it does not always cure the underlying condition; and, in the second place, patients recover from the ulcer without it. (4) The performance of a gastro-enterostomy at the primary operation adds to the mortality. Of Wilensky's series, 9 died; of these 3 had had gastro-enterostomy made at the primary operation. Of these 3, 1 died of shock, 1 of pneumonia on the seventh day, and the third died on the thirty-third day from a perforation of a coexisting ulcer. Of 8 patients treated by simple closure, 5 died. Of 10 patients treated by closure and immediate gastro-enterostomy, 3 died. Of 1 patient treated by tamponade, 1 died. Wilensky believes that, excluding the moribund cases, gastro-enterostomy is a most valuable procedure, not only as a help in securing the closure of the perforation, but also as a measure directed toward the underlying condition.

A Report of Nine Consecutive Operations for Perforated Gastric and Duodenal Ulcers.—SHEA (*Ann. Surg.*, 1916, lxiv, 410) says that all of the cases recovered. When seen early the diagnosis is easy. A positive diagnosis before operation was made in 8 cases. The most pronounced and characteristic symptom was pain—sudden, violent, and continuous. The abdomen was flat, retracted, and the rigidity board-like. The facial expression showed great distress and the respirations were shallow and rapid. In 5 cases the patient vomited, but this greatly increased rather than lessened the distress. Six patients gave a history of gastric disturbance, 3 gave no history of gastric trouble whatever. On opening the abdomen, when the perforation was found, the opening was cauterized with the actual cautery, a purse-string inserted, which, when drawn tight, readily closed the opening. In all cases drainage was provided. When there was considerable escape of fluid, the pelvis as well as the local site of perforation

was drained. Contrary to the procedure of many operators, no attempt was made to perform immediate gastro-enterostomy, because it was thought the added shock would prove detrimental in many cases, and also because it was felt that many cases of gastric ulcer recover after perforation. It is noteworthy that the majority of the patients remained free from subsequent gastric disturbances after treatment.

The Interpretation of Functional Renal Tests with Special Reference to the Significance of Minimal Excretion of Phthalein and Indigo-carmin.—BEER (*Ann. Surg.*, 1916, lxiv, 434) says that the last word in functional renal tests is still far off. The practical value of these tests becomes more and more evident as one succeeds in improving the interpretation of the facts elicited. In research along these lines one encounters puzzling contradictions, and it will take much more work to explain many of them. Why a given kidney (*e. g.*, a case of ureter stone) secretes more urea than its mate, but fails to excrete indigo-carmin while its mate does it normally, or why a patient dies of uremia while the phthalein output is normal or almost normal, illustrate some of the perplexities that one encounters. The important practical point in Beer's work is to arrive at an understanding of the significance of zero or minimal excretions. From a study of 17 cases, he concluded that: Extrinsic causes (usually obstructive in character) may lead to permanent symmetrical renal damage, evidenced by minimal or zero excretion of phthalein or indigo-carmin associated usually with high blood urea and high incoagulable nitrogen blood content. Operation in these cases will be of no permanent benefit, and even the slightest (in one case the passing of a cystoscope) may bring on a fatal uremia. Similar extrinsic causes may lead temporary renal damage evidenced by the same phenomena. Operation in these cases, particularly after adequate preliminary treatment, will be rarely followed by uremia. These two wholly different types of cases can be differentiated by removal of the usual causative factor, *i. e.*, relief of the obstruction, either by use of indwelling catheter, of regular catheterization, or by preliminary cystostomy under local anesthesia or gas. If the case is of the first type, no marked change in the renal output will result, whereas if the case is of the second type, the renal output will regularly improve. A similar low combined output may be caused reflexly (inhibitive or toxic) by more or less extensive disease of one kidney, while the other kidney is adequate and improves in its function after removal of its diseased mate or after relief of the pathological condition in its mate. A low combined output may also be due to bilateral intrinsic causes and improvement in these cases is possible only after operative attack on the kidneys, or the kidney, if single, under an anesthetic which has no injurious effect on the diseased parenchyma and provided no severe wound infection or other septic complications, etc., which overtax this parenchyma, develop.

The Treatment of Genital Tuberculosis in the Male.—CUNNINGHAM (*Surg., Gynec. and Obst.*, 1916, xxxiii, 3825) says that the material upon which his communication is based is from the postmortem and clinical data of the Boston City Hospital; the Long Island Hospital, where there is a large tuberculosis camp; private cases; and a survey of the

literature. In 4250 autopsy records he found 35 instances of tuberculosis of the epididymis, the most common lesion of the genital tract to be observed clinically, in which a microscopical examination as well as a gross description of the condition of the prostate and vesicles is recorded. He found 86 clinical cases of tuberculous epididymitis. A consideration of the literature, both postmortem and clinical, shows that tuberculosis of the genital tract in the male, is most common in the epididymis, and from the epididymis the disease extends along the vas, either by continuity or lymphatics to the vesicles and prostate. The postmortem and clinical findings show that the great majority of cases of genital tuberculosis have active tuberculosis elsewhere in the body, the infection in the genito-urinary tuberculosis being a secondary one. It must be considered that the majority of cases of tuberculous epididymitis have tuberculosis of the vesicles and prostate on the corresponding side, whether the condition can be demonstrated by physical examination or not. Cases of genital tuberculosis often have associated tuberculosis of the bladder and kidney, and a cystoscopic examination with catheterization of the ureter should be a rotation procedure, in each case, before the possibility of such associated infection can be eliminated. In the opinion of Cunningham, the best treatment for the local condition, in most instances, is to remove the scrotal focus by epididymectomy or castration, and this should be followed by injecting the vas with a dram of crude carbolic acid, with the hope of eradicating the disease from the genital tract. The destruction of the local focus is but the first step in the process of immunizing the patient against fresh outbreaks of the disease; and the hygiene and tuberculin should be made use of indefinitely, as they serve further to aid in a rational way, the immunizing power of the body against remaining lesions.

Perforation in Typhoid Fever. — Eddy (*Surg., Gynec. and Obst.*, 1916, xxxiii, 451), from a report of one case and an extensive study of the literature, concludes that: While perforation varies greatly in different epidemics, about 12 per cent. of the total death-rate is due to this complication. Perforation occurs in about 3 per cent. of all cases treated. It is relatively infrequent in children. Statistics show that 80 per cent. of total perforations occur in the lower ileum. The majority of cases perforate during the second and third week. Diarrhea is an important factor in its production. Acute abdominal pain in the course of typhoid should always be taken seriously. The sudden rise of blood-pressure is positive evidence of perforation, while an unchanged pressure is not of negative value. The importance of a careful study of the blood cannot be overestimated. The welfare of the patient depends upon our ability to differentiate between the symptoms of perforation and those of the resulting peritonitis. The treatment of perforation is surgical, and the death-rate is in inverse ratio to the length of time allowed to elapse before operation. Opiates are indicated as soon as perforation has taken place and should be continued until the peritonitis has become well localized.

The Treatment of Fractures by Nail Extension.—Dyas (*Surg., Gynec. and Obst.*, 1916, xxxiii, 478), on the basis of five cases treated by this method and a study of the literature, says that Steimann's nail exten-

sion in the treatment of fractures is less dangerous than the radical open operation. It enables the surgeon to exert the maximum amount of traction while using the minimum area for the attachment of the traction apparatus. It will bring about a reduction of the deformity in old cases where other methods fail. The technic is not difficult and can be mastered by anyone. Therefore the method is practical and can be used by the entire profession. It gives access to wounds in compound fractures, permits of infrequent dressings, and does away with unclean, infected fixation apparatus. The apparent brutality of the procedure is not real as the patients suffer no more by this traction than by any other method. The danger of infection is less than the danger of an open, radical operation. Hemorrhage may occur but can always be readily controlled by enlarging the incision and tying off the bleeding point.

THERAPEUTICS

UNDER THE CHARGE OF

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Splenectomy in Pernicious Anemia.—LEE, MINOT and VINCENT (*Jour. Am. Med. Assn.*, 1916, lxvii, 719) give their findings regarding the mode of action of splenectomy as a therapeutic procedure—particularly with regard to its effect in stimulating the bone marrow to produce new blood. They believe that splenectomy in pernicious anemia has in nowise a specific stimulating effect on any one portion or any one function of the bone marrow. It apparently acts grossly on all portions, though the effects are seen at different periods of time in relation to the operation. They attribute the temporary improvement in pernicious anemia after splenectomy to two factors: (1) an associated diminution in the blood destruction; and (2) the associated increase in activity of the bone marrow. They do not attempt to explain the precise mechanism by which splenectomy brings about an increased activity of the marrow. Certain stimulating effects after splenectomy are seen almost immediately, as in the case of the increase in the polymorphonuclear leukocytes. The increase in the platelets tends to occur somewhat later, and the main increase of the reticulated cells, when it occurs, seems to be inaugurated still later. This effect on the part of the bone marrow which forms red cells is much more difficult to bring about and also is slower. Splenectomy seems to result in the greatest stimulation of the bone marrow of any known therapeutic measure. It acts on the whole bone marrow and not only on the portion that forms red cells. However, splenectomy does not alter the essential course of the disease. While more constant stimulating effects are seen after splenectomy, yet they can roughly parallel

any individual case of bone marrow stimulation after splenectomy with a case of bone marrow stimulation that occurred either spontaneously or after transfusion. It is evident that from splenectomy one can attain stimulation but once. Transfusion, while perhaps of less constant and of less active effect, has two great advantages. It is relatively simple and can be repeated a number of times. Transfusion does not modify the destructive agencies at work in pernicious anemia. These considerations must be carefully weighed in advising any therapeutic procedures in this disease.

The Use of Emetin.—Reid (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 375) says that the predominant use of emetin is in the treatment of amebic dysentery, and the history of the empirical use of ipecac, combined with the demonstration of the specific amebicidal action of emetin, places its use here on a solid footing. In using emetin in dysentery it is important to recall that if there is to be any benefit, it will usually appear early, ordinarily by the third or fourth day. Emetin seems specific in direct proportion to the acuteness of the attack. Chronic dysentery and ameba carriers, as a rule, are influenced by emetin directly, although even here there are certain favorable reports. Emetin has also a very definite use in the presuppurative stage of amebic abscess of the liver. After actual abscess formation, emetin may be a valuable adjuvant to surgical treatment. Emetin has been advocated lately for the treatment of pyorrhea. It will, without doubt, cure the amebic infection found associated with pyorrhea but definite proof that amebæ are the cause of pyorrhea is still lacking. The use of emetin as a remedy for hemoptysis in pulmonary tuberculosis apparently originated in France. Certain clinical observations seem to justify the belief that emetin is a useful drug in hemoptysis but the treatment is entirely empirical and does not rest upon any solid foundation. Emetin has been tried and recommended for a great variety of diseases but very few of its other applications will bear the test of careful experimentation. It has proved serviceable in the treatment of certain other diseases caused by animal parasites, especially protozoöns, but the chief use of emetin is dependant upon its amebicidal action.

Peripheral Neuritis following Emetin Treatment of Amebic Dysentery.—Wilgore (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 380) reports seven cases of peripheral neuritis following the use of emetin in amebic dysentery. He says that peripheral neuritis after emetin is not uncommon. The symptoms most commonly met with in postemetin neuritis are muscular pain and weakness, usually most pronounced in the legs, sometimes going on to paresis. The neuritic symptoms often develop after the emetin injections have been stopped, and may grow progressively worse for some time, with no more administration of the drug. The total amount of emetin necessary to produce neuritis varies greatly. The prognosis is good; the symptoms clear up gradually, usually over several weeks, leaving no traces apparent. Experiments, made by Wilgore, suggest that peripheral neuritis may be produced in healthy dogs by emetin.

Three Cases of Entameba Histolytica Infection Treated with Emetin Bismuth Iodid.—Law and Dobell (*Lancet*, 1916, cxci, 319) say that evidence derived from their own cases and from cases reported by Dale has convinced them that emetin bismuth iodid is far more efficacious than emetin hydrochlorid, given hypodermically, in removing the cysts from the feces of chronic carriers. The authors recommended giving the remedy in a single dose of three grains—this representing a little more than one grain of emetin—once a day with the evening meal, and never on an empty stomach, as was customary with ipecac. Such a dose is to be given on five successive days—and the full course of treatment recommended is twelve doses of three grains each. One disadvantage is that this new emetin compound produces much more disagreeable symptoms than emetin hydrochlorid given by the needle. Nausea, vomiting and diarrhea were the untoward symptoms produced. Three cases are reported in detail as types of amebic infection for which method of giving emetin is recommended.

Late Results of Splenectomy in Pernicious Anemia.—Krumbhaar (*Jour. Am. Med. Assn.*, 1916, lxvii, 723) says that the striking improvement that has been shown to follow removal of the spleen in such diseases as hemolytic jaundice and Banti's disease has naturally led to an extension of this clinical procedure to allied conditions. In 1913 three investigators, Eppinger, Decastello and Klemperer, working independently, applied splenectomy to the relatively common and grave disease, pernicious anemia. It is interesting that Eppinger was led to adopt this procedure by observing after splenectomy a diminished output of urobilin and other evidences of decreased hemolysis. Decastello, on the other hand, had noted the improvement that followed splenectomy in the related conditions, hemolytic jaundice and Banti's disease; whereas Klemperer was influenced by the clinical observation that splenectomy for such conditions as rupture of the spleen was in some instances eventually followed by polycythemia. Krumbhaar reviews critically the reported cases of splenectomy as a therapeutic measure for pernicious anemia in order to determine how valuable splenectomy has thus far proved to be in pernicious anemia. Of the 153 patients studied, 19.6 per cent. died within six weeks; a distinct improvement in the clinical condition and in the blood picture occurred in 64.7 per cent., and no improvement in 15.7 per cent. The rather high postoperative mortality (practically 20 per cent.) may be due to poor choice of cases in the early series. As a much greater proportion of the more recent cases has survived the operation, the true postoperative mortality is probably much less than 20 per cent. Of the individuals who showed improvement shortly after operation, nearly two-thirds of the total number, a large number have failed to maintain this improvement, or have since died in a relapse or from intercurrent disease. Although a few have continued in good condition during the period of observation (over two years), in no case can it be said that a cure has been effected, and the blood of these individuals continues to show many of the characteristic signs of pernicious anemia. On account of the improvement that follows splenectomy, it would appear to be not only a justifiable, but in many cases an advisable, procedure; but in no case should a cure be promised or the operation undertaken except

under the most favorable conditions. The best results are obtained if the operation is preceded by one or more transfusions, and those patients who relapse after operation may still be greatly helped by transfusion. Whether or not transfusions would have produced equally good results in the absence of splenectomy is a question that cannot at present be decided. The most favorable results may be expected in individuals who have not passed the fifth decade in whom the disease has not progressed for more than a year, and who have a relatively good blood picture (that is, an anemia that is not of too extreme a degree or of the steady, progressive type). Individuals with enlarged spleens have done better than those in whom the spleen was small or of normal size, as have also those suffering from an anemia characterized by excessive hemolysis. The opposite of these conditions should be considered as unfavorable factors, as should also the existence of spinal cord symptoms or the presence of an aplastic bone marrow.

PEDIATRICS

UNDER THE CHARGE OF

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A Case of Egg-poisoning (Anaphylaxis).—EDLESTON (*Practitioner*, vol. xcvii, No. 4) reports a well-marked case of egg anaphylaxis, first noticed at the age of twelve months. The first attack began after taking a few teaspoonfuls of custard pudding. The symptoms were those of an acute gastritis with frequent vomiting. She was given albumen water and rapidly collapsed. All food was then withdrawn, and later chicken broth was substituted, under which treatment she soon recovered. Eggs in every form were avoided after this, but on several occasions when given accidently, the symptoms have usually been as follows: The child complains of feeling ill, and wants to lie down; the pupils dilate, and vomiting follows. In some attacks chemosis of the conjunctivæ supervenes. Urticaria has occurred in some of the attacks. On one occasion, while standing near her mother, who was beating an egg on a plate, a splash of egg flew into her eye. This was followed by rapid swelling, so that the eye could not be opened, but no other symptoms of poisoning followed. The child is now eleven years old, and is still as sensitive as ever to the poison.

A Case of Prolonged Hyperpyrexia in a Child with a Mid-brain Tumor.—TURNER (*Brit. Jour. Child. Dis.*, September, 1916) reports an unusual instance of prolonged hyperpyrexia associated with a tumor in the mid-brain. The child, aged one year and six months, was admitted to the hospital with the provisional diagnosis of meningitis. There was opisthotonos, squint, and convulsions on the day of admission. Hydrocephalus was present, the fontanelle being very tense.

Temperature was 103° on admission, pulse 172, and respirations 60. About two and a half ounces of clear colorless fluid was withdrawn by lumbar puncture, under great pressure. The fluid showed no increase in albumin; no cells were seen, and the cultures were sterile. The child lived for thirty days after admission, in a state of extreme rigidity. Lumbar puncture was repeated twice, the cells, mostly mononuclears, being more numerous than normal. The Wassermann reaction was negative. There was a low grade optic neuritis. The temperature was the most remarkable feature of the case. For a period of ten days it showed very great variation; once, or sometimes twice during twenty-four hours it would rise to 105°, 106° or 107°, and then rapidly falls so that in eight to twelve hours it would be normal or subnormal. The maximum was reached one morning at 7 A.M. when the axillary temperature was 109°, and the rectal 111°. Postmortem a solid rounded tumor was found situated in the mid-line in the region of the corpora quadrigemina. It did not involve the pons, optic thalami, or the cerebellum, but was pressing forward into the aqueduct of Sylvius, causing a block, with resulting distention of the third and lateral ventricles. Microscopically the section of the tumor showed it to consist of numbers of round cells, uniform in size, with but little intercellular substance. In parts the growth had undergone cystic degeneration, leaving a hyaline material without cell element: The author was unable to find a similar case recorded in the literature, and apart from the terminal hyperpyrexia of cerebral lesions, there is no mention to be found of any such condition occurring in cases of cerebral tumor.

The Bacteriology of the Urine in Healthy Children and those Suffering from Extra-urinary Infections.—BEELER and HELMHOLZ (*Am. Jour. Dis. Child.*, October, 1916) report their bacteriological findings of catheterized specimens of urine taken from thirty girl infants and from thirty-one girls over two years of age. In 118 specimens of carefully catheterized urine from these 61 girls, 61 were sterile and 57 contained bacteria. Of those from normal infants, 13 were sterile and 11 contained bacteria. Of those from extra-urinary infections in patients under two years of age, none were sterile and 24 contained organisms. In those from girls over two years, 38 were sterile and 22 contained bacteria. The number of bacteria found in the urine of children under two years was considerably larger than in those over two years. This may be explained by the fact that in the older children one can cleanse the urethral orifice much easier than in the infant and introduce the catheter directly into the urethra. The bacterial flora was practically the same in both series, Gram-positive cocci and diphtheroid organisms predominating, the former being present in practically every case in which any organisms were found. In no instance were Gram-negative bacilli found in such numbers in both specimens that it seemed probable that it was more than an accidental contamination from the urethra. The conclusions the authors draw are, (1) that organisms of the colon bacillus group are not normal inhabitants of the female urethra; (2) that in extra-urinary infections occurring in the first two years of life the colon group of bacilli are frequently found in the urethra (one-third of the cases); (3) that in girls over two years of age the urine is almost free of organisms, and in their series entirely free from bacilli of the colon group (eighteen normal, twelve other infections).

OBSTETRICS

UNDER THE CHARGE OF

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Modern Obstetric Surgery.—MUNRO KERR (*Brit. Med. Jour.*, July 15, 1916) has recently published a third edition of his book on midwifery. This book gives an excellent account of modern obstetric surgery from the English standpoint. Where tetanic contraction of the uterus occurs in complicated labor, the question arises as to what method of delivery is safest for mother and child. To the obstetrician, Cesarean section in clean cases where the child is living, suggests itself as the best method of treatment. Where, however, the case is not clean, or suspected, a full dose of morphin and atropin are first given, followed by an interval of rest, and then delivery by craniotomy. Fibroid tumors complicating pregnancy must be managed in accordance with the size and location of the tumor and other conditions present. Wherever possible enucleation is preferred. Upon one important subject the author speaks with decision. Appendicitis during pregnancy, labor, or the puerperal period is considered a highly dangerous complication. The author would treat all such cases on strictly surgical lines without regard to the existence of pregnancy. In this the reviewer fully agrees, and his opinion is based on experience and clinical observations. While the proposition to enlarge the pelvic girdle by operation is in some respects attractive, the procedure has a limited field of usefulness, but it is only in exceptional cases that good results will be obtained. One of the most difficult problems for the obstetrician is the management of a case requiring delivery by section where the child is alive and the mother infected. Shall one choose craniotomy upon the living child or shall one deliver by section followed by hysterectomy? The author is convinced that craniotomy should sometimes be chosen even though the child is alive. He raises the question whether hysterectomy really saves mother and child. He believes that we do not save mothers, for the maternal mortality from hysterectomy and craniotomy in infected cases is almost identical. A few children are saved by hysterectomy, but young mothers may be sterilized who losing the first child might subsequently produce several others. The flaw in this argument lies in the fact that Kerr has evidently not left the stump of the septic uterus outside the peritoneal cavity in treating these infected cases. Hysterectomy, followed by dropping of the septic stump, has a very considerable mortality from sepsis, while hysterectomy followed by leaving the stump outside the peritoneal cavity, whether it be stitched into the tissues or held by a clamp, has a very low mortality. For the various kinds of extraperitoneal section and section through a peritoneal fistula he has no praise. He has had no experience, believes that this method has no advantage over classical section, and will disappear and be forgotten

unless experience shows that the scar in the lower segment is much stronger than the one in the upper part of the body of the uterus. One would scarcely expect, in the present condition of affairs, an operation largely perfected in Germany to be popular with a British obstetrician. The author regards vaginal Cesarean section as an operation of great value, but used too freely. Up to the twenty-fifth week of pregnancy it is the best way of rapidly emptying the uterus, after the abdominal route is preferred. Vaginal section should never be chosen in placenta previa. The author would perform abdominal Cesarean section in placenta previa in elderly primiparæ with active bleeding, undilated cervix, and viable child. Despite the recent literature upon the subject, in accidental hemorrhage the author clings to the tampons where the membranes are intact, and the bleeding external, but what he would do when the placenta separates with retained blood, is not clear. He does, however, condemn the use of the bags, the Bossi, and similar dilators. He admits that in concealed hemorrhage section may be necessary, and prefers vaginal operation. In the field of English obstetrics Kerr's book is easily the best upon obstetric surgery, and we welcome a new edition and learn with great interest the views of this author.

The State and the Birth Rate.—The question of what can be done to prevent a falling birth rate has been recently studied by the authorities of the British Empire, and the local government board has recently received the report of the commission appointed to inquire into the decline of the birth rate of England. In the London letter to the *Journal of the American Medical Association*, dated July 3, 1916, and published in the *Journal* for July 29, 1916, it is stated that this report advised that the sale of certain drugs widely used for the purpose of abortion should be made illegal. Measures must also be taken to lessen the ravages of venereal disease. The most difficult problem consists in educating the public opinion to condemn effectively vice which brings about disease. It is also necessary to improve the living conditions and adjust the burdens of taxation for that class of the population capable of producing the best children, and caring properly for them. The large, and socially valuable middle class should receive especial attention from this standpoint. It is also urged that immigration to healthy portions of foreign possessions be encouraged, and the taxation should be adjusted as to bear least heavily upon those who are rearing families.

An Infant Mortality Rate of Zero.—A community in which the infant mortality has been reduced to zero presents much of interest in view of the increased value at present attributed to infant life. In a paper published in the London *Lancet*, May 6, 1916, Moore, an English medical health officer, learned that Villiers-le-Duc, a little commune in the south of France, had an infant mortality rate of zero for ten years. This seemed incredible, but on applying to the French Academy of Medicine, official documents showed that between 1893 and 1903 no child under one year of age had died in this commune, and no mother had died in childbirth. The infant mortality for the preceding ninety years had been from 20 per cent. to 30 per cent. except from 1854

to 1863, when it fell to 15 per cent. During this time a mayor was elected who was interested in public health and the care of children, and although not a physician he did his utmost for the health of the people. The low death rate just described has been obtained by the son of the former mayor, who studied medicine to obtain knowledge with which to carry out plans for the welfare of the people. In this commune every pregnant woman, married or unmarried, who needs help can apply to the village authorities, and must do so before the seventh month. The patient may select a competent midwife, who must examine her, and if albuminuria, abnormal presentation, or other abnormalities be discovered the midwife must notify the village authorities, who then causes the patient to select a physician. If the patient remains in bed six days after her confinement she has an allowance from the village for her expenses for each day. Mothers or nurses who can show a healthy nursing child a year old are entitled to municipal grants. Other regulations were made providing for the sterilization of milk and the welfare of infants placed out to nurse. It is true that these statistics are obtained in a small village with simple rural conditions, nor are the statistics available of the population, number of births, and changes in population due to immigration. These facts make the statistics less valuable and others more accurate. They are, however, still interesting, and the simple regulations enforced and their success are certainly suggestive.

The Internal Secretion of the Pancreas in its Relation to Pregnancy.—Falco (*Annali di ostetricia*, No. 1, 1916) has made researches upon animals in the pregnant condition, extirpating the pancreas and then studying the condition of the animal. He finds that the removal of the pancreas seems to diminish somewhat the growth in function and activity of the cells in Langhan's layers of the syncytium. The extirpation of the pancreas does not cause pregnancy to terminate, nor does it produce glycosuria. It naturally produces the symptoms of pancreatic diabetes. This does not seem to influence the internal secretion of the fetal pancreas, as evidently the abnormal products formed in the mother's body are disposed of by the fetus and by the placenta. The placenta evidently has an important part in the disposition of physiological products in the mother and fetus.

Viburnum Prunifolium to Prevent Abortion.—In recent numbers of the *Journal of the American Medical Association* has appeared the testimony given in a suit brought against the *Journal* in which various statements are made concerning the efficiency of viburnum in preventing or checking abortion. The reader of these conflicting statements must judge for himself. So far as the reviewer's experience goes he has no positive and accurate evidence that viburnum prevents or stimulates uterine contraction, or prevents or stimulates abortion. He has used it, but always in compounds with other drugs whose actions are well known. So far as his experience goes two medicinal substances lessen or prevent contraction of the uterus. One comprises that class acting as sedatives to the general nervous system, of which bromide of sodium is a good example. The other is opium, the most reliable drug which we possess in preventing uterine contraction and lessening its vigor.

GYNECOLOGY

UNDER THE CHARGE OF

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Carcinoma of the Uterus in a Child.—A most remarkable case of adenocarcinoma of the uterus occurring in a child two and a half years of age has been reported by ADAMS (*Brit. Jour. Child. Dis.*, 1916, xiii, 266). The parents were healthy, and this was their first child. It appeared healthy and well nourished, but for three weeks before admission to the hospital there had been a bloody vaginal discharge, increasing in amount. There was no pain, but the mother had noted some fulness of the abdomen; on examination a palpable tumor was found in the hypogastrium, lying apparently between the bladder and rectum. At operation a rounded, cystic growth, the size of half a tennis ball, was found obscuring the position of the uterus. A portion of the mass was removed, but it was too adherent to permit of complete extirpation. The vaginal hemorrhage reappeared shortly after the operation, gradually increasing in amount; the child lost ground steadily, and died in two months. At autopsy a large mass was found occupying the centre of the pelvic cavity, closely adherent to the bladder and rectum, representing the uterus, which was in large part transformed into breaking-down tumor tissue. Histologically it proved to be a carcinoma apparently arising from the glandular epithelium of the corpus uteri. At one point the growth had penetrated the bladder wall. Unfortunately the author presents no illustration of either the gross or microscopic appearances of this remarkable specimen.

Radium Treatment of Uterine Cancer.—Practically all reports upon this subject from this country must be considered as more or less preliminary at present, as very few workers can report cases of five years' standing or longer; it is well, however, that results should be recorded from time to time as the work in various clinics progresses, provided the reports are modified as time goes on. Taken, therefore, purely in the light of a preliminary report, a recent short paper by J. and J. L. RANSOHOFF, of New York (*Ann. Surg.*, 1916, lxiv, 298), presents some exceedingly encouraging results so far, none of their cases having been followed for more than two years, however. They report having used radium in 25 cases of uterine carcinoma; of these, 11 appear clinically well, 3 of these having been followed for two years, the remainder for periods of six months to almost two years. Of these 11 cases, 8 were inoperable, and 3 were operable from a technical stand-point, but because of other conditions operation was considered inadvisable. Even in the cases where a clinical cure was not obtained, some benefit was obtained in every instance, the experience of these authors in this respect having been apparently more fortunate than that of most other workers with radium, nearly all of whom report a certain percentage of cases in whom not only no benefit, but even some apparent harm, is seen following treatment. The authors report a couple of instances

in which there was almost magical disappearance of extensive vaginal masses, with correspondingly great improvement in the patient's general condition. In a few instances the patients have complained of pain in the rectum, sometimes quite severe, coming on subsequent to radium treatment. The authors suggest that this may be due to the formation of scar tissue, though this they cannot definitely demonstrate. They advise very strongly against attempting radical operation in cases clinically cured by radium.

Cystitis in Elderly Women.—Under the title "Cystitis Senilis Feminarum," CHARLTON (*Surg., Gynec. and Obst.*, 1916, xxiii, 371) calls attention to a condition which he considers to be an important clinical entity, but which has received very little attention in the literature, namely a peculiar type of cystitis, presenting characteristic cystoscopic changes, and occurring with very few exceptions in elderly primiparæ. The history is usually that a woman well past the menopause, mother of several children, in fairly good general health, gradually begins to notice undue frequency of urination, with burning and tenesmus. There is no acute onset, but from time to time there may be severe exacerbations, causing marked impairment of the general health. Such sharp attacks may persist for weeks, followed by months of comparative comfort. The urine may show a moderate amount of mucus, with some pus, but is never grossly thick and ropy. Bacterial findings have been entirely inconstant, and the tubercle bacillus does not appear ever to be the causative factor. The author believes, therefore, that it is probably not due to a specific infection, but is a condition developing after many different bacterial onslaughts in bladders already weakened by the process of senile decay. He has found that almost without exception the condition is common to the bladder, vagina, and rectum simultaneously. The vaginal changes are those of ordinary senile vaginitis. The rectal mucosa varies in its appearance in these cases from multiple punctate erosions to large distinct punched-out areas of ulceration on an otherwise normal pink velvety base. The cystoscopic appearance is primarily that of numerous vesiculopapillary elevations, seen especially during the acute exacerbations, and presenting the picture commonly designated as bullous edema; in two cases the similarity to miliary tubercles was striking. During the interval the vesicular eruption disappears and gives place to a patchy, ecchymotic appearance of the bladder mucosa, with unbroken epithlium. The treatment of these cases is best carried out, according to Charlton, as follows: (1) The best of general and hygienic care. (2) Hot boric irrigations of the bladder, which may be supplemented with instillations of argyrol. Vigorous local treatment, such as the application of strong silver solutions, is to be condemned. (3) Alkaline vaginal and rectal douches. (4) Administration by mouth of *pure liquid guaiacol*, given in 5- or 10-drop doses after each meal. This drug the author has found to possess almost specific properties; it almost always brings remarkable and quick relief from the frequency of urination, tenesmus, and burning of which these patients complain so bitterly. Its use is largely empiric, though an attempt has been made to explain its effect on the ground that the benzoic acid radical is broken up and eliminated by the kidneys as hippuric acid, which being a normal urinary acid may play some definite part in the relief.

OPHTHALMOLOGY

UNDER THE CHARGE OF
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Optic Nerve Atrophy in Chiasmal Lesions.—WALKER and CUSHING (*Arch. Ophth.*, xlv, 407), from their studies in this condition, conclude that, despite the so-called atrophic pallor of the disks with visual field defects from lesions in the chiasmal regions, the histological examination of the nerves fails to show the expected degree of fiber degeneration unless the process has been of long duration. The atrophy in the tracts considerably antedates that in the nerves, where the fibers may be preserved by their retinal ganglion cells for several years after complete functional blindness has occurred. Their cases serve to illustrate the fact that in the presence of chiasmal pressure of known long duration associated with sharply cut hemianopsias, even when the ophthalmoscope shows the pallor of presumed optic atrophy, there may be no corresponding sharp delimination of the areas of atrophy in the cross-sections of the nerves. This at first sight would appear to be an inconsistency, but their more accurate perimetric findings with graded disks show that, after all, the boundaries of the seeing areas are less sharply cut than had previously been supposed, and perhaps correspond after all with the diffuse picture in the nerves.

Hemeralopia (Night-blindness) in Soldiers.—WEEKERS (*Arch. d. Ophth.*, March–April, 1916, p. 73) calls attention to this condition as a novel phenomenon of war. He finds that it is frequent among soldiers—as high as 10 per cent. of those sent for ocular complaints. The cases are specially numerous during the long nights of winter. Errors of refraction are frequent. Many had been affected with the same condition as a congenital anomaly before the outbreak of the war. The malady is provoked by several factors, although of unequal importance. First of all is to be noted the unphysiological mode of life in the trenches which is nocturnal, fatigue, nervous upsets, anxiety, overexertion. Eye-strain from errors of refraction is also an important factor. Finally, the unvarying diet, preserved foods, dazzling from bright lights, etc., are also involved. The treatment should be directed to the cause. One of the most efficacious means is careful correction of all refractive errors especially astigmatism: smoked glasses during the day form a valuable adjuvant. Varied diet and as much rest as possible should be prescribed. The prognosis is favorable.

A Suggestion as to the Cause of Myopia.—WOOD (*Ophthalmoscope*, 1916, xiv, 302) suggests that the marked difference between the ciliary muscles of the myope and hypermetrope may be the cause of the myopic

refraction and not the effect as is generally believed. He quotes authorities to the effect that the difference in structure is present at birth and hence cannot be the result of disease, mechanical pressure, or disuse. He argues that the pumping action of the ciliary muscle is at fault, and that it is this which favors the changes which lead to brachymetropia. He remarks upon some of the causes (strain of convergence, spasm of accommodation, etc.), frequently adduced as leading to myopia, and believes that the progress of investigation has disposed of most of them. He thinks that if sections from the eyes of an individual with monocular myopia were to show a difference in the ciliary muscle on each side, his case would be greatly strengthened. Such cases can assuredly be found, and deserve to be studied pathologically.

Contusion Hypotony.—COLLINS (*Ophthalmoscope*, 1916, xiv, 348) discusses that form of hypotony which occurs after contusions of the eyeball without perforation; this form of minus tension is well-known but has been the subject of but little discussion. The duration of the diminished tension varies considerably; in the majority of cases it disappears in a few days; in others not for several weeks; and in some cases it would appear to be permanent. The causes of such hypotony may be various and more than one cause may be active at the same time. When of short duration, it is probably due to increased excretion of the intraocular fluid through the expanded normal channels of exit; or, possibly, to some arrest of secretion from paresis of the vasoconstrictor nerves. When of long duration it may be due to (*a*) the formation of new channels or exit from the anterior chamber either from an internal scleral rupture or rupture of the pectinate ligament; (*b*) the cutting off of blood supply to the ciliary body from rupture of the anterior ciliary arteries; or (*c*) possibly detachment of the pars ciliaris retinæ. If extensive hemorrhage into the anterior chamber be present, either the canal of Schlemm has been opened by an internal scleral rupture or the anterior ciliary arteries have been torn across from cyclodialysis. The latter is shown to be the cause if, after absorption of the blood, a portion of the iris has disappeared from view as though an iridectomy had been done. A translucent area appearing after some time just outside the sclerocorneal margin like that in a cystoid cicatrix, indicates an incomplete internal rupture. If the anterior chamber, without extensive hemorrhage, becomes markedly deepened in the whole or part of its circumference there has probably been a rupture of the ligamentum pectinatum, limited to the pillars of the iris, and of the ciliary muscle, prolonging the angle of the anterior chamber outward. If the lens is dislocated laterally, and the retina detached, the vitreous has probably come forward into the circumlental space, and may have dragged the pars ciliaris retinæ away from the pigment epithelium.

Miotics after Mydriatics.—GIFFORD (*Jour. Am. Med. Assn.*, 1916, lxvii, 112) calls attention to the slight but real danger of exciting an attack of glaucoma by the cycloplegic (homatropin) employed to measure the refraction. He suggests that eserin solution should be instilled not only after the examination, but should also be given for use at home

until the effect of the mydriatic is gone. He advises that the patient receive a small quantity of eserin solution, one grain to the ounce, a drop of which is to be instilled into the eye with the butt end of a match or toothpick. He reports several cases where an attack of acute glaucoma was excited by the cycloplegic.

Enlargement of the Blind-spot with Gradenigo's Syndrome.—VERDERAME (*Ann. di ottal.*, 1916, xliv, 538) summarizes Gradenigo's researches which led to the syndrome bearing his name—a disease-complex first described in 1904; the syndrome is characterized by a purulent otitis media with paralysis or paresis of the sixth nerve of the same side. Of the 6 cases observed by Gradenigo, 5 recovered, the other terminated fatally from purulent leptomeningitis. He refers the condition to a circumscribed purulent or simply serous leptomeningitis, which may recover spontaneously, or after operation through the temporal bone, but which sometimes spreads so as to lead to a fatal result. The otitic symptoms are due to infection of the tympanic cavity, which infection may spread to the base of the middle cranial fossa leading to paralysis of the sixth nerve. In a case of this kind, Verderame observed moderate mydriasis, enlargement of the blind spot and slight contraction of the color field; the only ophthalmoscopic signs were hyperemia of the disk and of the retinal vessels. At the end of a week all symptoms had disappeared except the mydriasis; of the significance of which latter symptom the author was in doubt.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Immune Reactions in Scarlet Fever.—In an earlier work, G. F. and G. R. DICK (*Jour. Infect. Dis.*, 1916, xix, No. 2) reported the results of anaërobic culture from the blood, lymph, spleen, throat and mouth secretions in scarlet fever. Before further study of the organisms obtained in these cultures, they decided to test the various tissues from which these organisms were grown in order to determine whether or not a virus either ultramicroscopic or failing to grow with the cultural methods used was present as the primary cause of the disease. The secondary importance of the organisms obtained could then be demonstrated. The following tests were made on the blood and the results noted: Since antigens in the body fluids

have been found by means of complement-fixation, this test was applied, but although the tests were carried out in various ways, there was no evidence of complement-fixation. The blood of scarlet fever patients was tested for toxicity by injecting it into guinea-pigs with the result that it was found to be more toxic while the patient is acutely sick than during convalescence. The blood was also tested for the presence of living virus by the potassium tellurid test. In the sera of six cases of scarlet fever there was no precipitation of tellurium more marked than in the negative control tests, although the positive controls showed marked precipitation in every instance. The spleen of a child who had died on the second day of scarlet fever was used to prepare antigen, and complement-fixation tests were made with the sera of six cases of scarlet fever. No tests showed complement-fixation. Cutaneous tests similar to tuberculin tests made with extract from the same spleen in four convalescent scarlet fever patients and four diphtheria patients gave uniformly negative results. In testing the tissue from the lymph glands, an antigen was made from lymph glands from various parts of the body of a patient who had died on the second day of scarlet fever and fixation tests carried on with the same sera as in the spleen tests with uniformly negative results. Cutaneous tests with lymph gland extract were negative in three cases of scarlet fever. In the last series of tests, mucus from the mouth and throat was used as antigen for the complement-fixation tests. In sera from four cases of scarlet fever in various stages of convalescence, each used with a different antigen, there was no complement-fixation. In the fifth case, there was a slight fixation of complement with 0.3 c.c. of antigen, but with the serum of a sixth case, the same antigen failed to fix complement. The results of the complement-fixation tests with organ extracts harmonize with the results obtained by some observers but are at variance with those obtained by others. The authors suggest in their summary that it may possibly be that insufficient concentration of antigen explains the negative results and therefore it seems desirable to further continue the study of the immune reactions of cultures obtained from scarlet fever.

Agglutinins after Typhoid Immunization.—Robinson (*Jour. Med. Research*, 1915, xxxii, 417) states that great individual differences occur concerning serum reactions during typhoid immunization. Agglutinins begin to increase in the blood from four to eighteen days after the first inoculation. The blood gives a positive agglutination at 1 to 60, on the average, sixteen days after the first inoculation. Ascole (*Riforma med.*, Naples, 1915, xxxi, 645) states that the serum gives a positive agglutination reaction in every one who has been vaccinated against typhoid.

Anaphylactic Reactions between Proteins from Seeds of Different Genera of Plants.—Wells and Osborne (*Jour. Infect. Dis.*, 1916, xix, No. 2) conclude that since chemically similar proteins from seeds of different genera react anaphylactically with one another, while chemically dissimilar proteins from the same seed in many cases fail to do so, we must conclude that the specificity of the anaphylaxis reaction depends upon the chemical structure of the protein molecule.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Lipoma Myxomatodes.—Although essentially a case report from the standpoint of the pathologist, ROBERTSON (*Jour. Med. Research*, 1916, xxxv, 131) in reality presents a monograph on lipoma myxomatodes The first accurate description of this tumor was that by Virchow in 1857. He included all tumors containing elements resembling the jelly of Wharton or embryonal connective tissue under the term "myxomata," and the particular variety which also showed lipomatous elements he named "myxoma lipomatodes." A tabulated analysis of fifty-one cases collected from the literature is published. In surveying this table, statistical generalizations as to age, sex, sites of election, frequency in such sites and weight of the growth are easily made. It is also known that the usual locations of pure lipomata are singularly free from lipoma myxomatodes. One-third of the cases in the literature have shown malignancy which, in view of the embryonal types of tissue concerned, is to be expected. The statistics show that over half of the cases had existed for one to five years. This would indicate that sarcomatous change had occurred in a primarily benign growth. The tumor in the author's case was removed from the lower leg of a man, aged fifty-four years. It was not connected with the skin and had given no symptoms, although it was present for fifteen months before operation. The tumor was encapsulated. The length was 24.5 cm. and the widest diameter was 6.5 cm., from which the mass tapered down to 2.5 cm. in width at either extremity. The growth was irregularly lobulated, the divisions being formed by fibrous trabeculæ. The various lobules varied widely in consistency. On cross-section, three distinct types of tissue could be identified by gross examination. They were (*a*) myxomatous, (*b*) fatty, (*c*) a mixture of the two. Microscopically, these characters were well borne out. The myxomatous parts showed a stroma of stellate embryonal connective-tissue cells, while the greater part of the tissue was made up of large spaces filled with a substance which gave the usual reactions for mucus. The fatty parts showed a myxomatous stroma, supporting many fat cells resembling the adult type, as well as numerous embryonal fat cells. In the area of apparent mixture of the two tissues, embryonal fat cells were numerous. The usual myxomatous stroma was found, containing many spaces filled with mucus, as in the purely myxomatous portions. The author relied

on the presence of true mucoid material regardless of its origin to place the growth in this group. Regarding the fatty tissue, he considered it reasonable to expect the combination of this with the myxomatous tissue since both are essentially embryonal in character, though of independent mesoblastic origin. He doubts the possibility of myxomatous connective tissue taking on fatty change. The question of malignancy is dealt with cautiously. The frequency of local and metastatic recurrences is to be remembered, as well as the embryonal types of cells making up the growth. In his case, however, the author feels that the definite encapsulation and the quantity of fairly adult fatty tissue are against a recurrence.

The Function of the Bile in Preventing Putrefaction.—Under normal conditions bacteria play an important part in bringing about disintegration of nitrogenous materials of the intestine. Even in health there is a considerable variation in the character and amount of decomposition thus brought about. Metchnikoff and others believed that the products of decomposition developing within the bowel had much to do with organic changes and ill health. For a considerable time it has been claimed that the bile had a direct inhibitory effect upon the growth of the intestinal bacteria and by this means undue putrefaction was held in check. Newer studies have indicated that, save with a few bacteria, bile has little influence upon their growth. Nevertheless, it has been well established that under conditions of bile stasis when little or no bile flows into the intestine, abnormal decomposition of the intestinal contents occurs. ROGER (*Ann. de l'Inst. Pasteur*, 1915, xxix, 545) has recently investigated the problems of determining the influence of bile upon intestinal bacteria and their secretions. He found that bile inhibited the growths of anaërobes but had no marked influence upon the growth of the other intestinal forms. He found, however, that bile had an inhibitory effect upon the fermentative secretions of various bacteria as well as diminished the toxicity of their products. The tests were carried out with various bacteria in the test-tube, while the antitoxic qualities of bile were observed in rabbits. He concludes that the antagonism of bile to putrefaction is not so much dependent upon the inhibition of bacterial growth as upon its neutralizing effect on the secretions of bacteria. It is also possible that bile not only destroys the bacterial ferments but also renders inert their products of decomposition.

ERRATA.—Vol. clii, No. 5, November, 1916, p. 757, after the word "solution" at the end of line 40 the following should be inserted: "of albumose intravenously. The authors were able to confirm these results using a solution."

Ibid., p. 779, line 14: "hemorrhagic" should be omitted; line 15, "vesicules" should be "vesicles."

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DR. GEORGE MORRIS PIERSOL, 1913 Spruce St., Phila., Pa., U. S. A.

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